



(12) Translation of
European patent specification

(11) NO/EP 3022175 B1

NORWAY

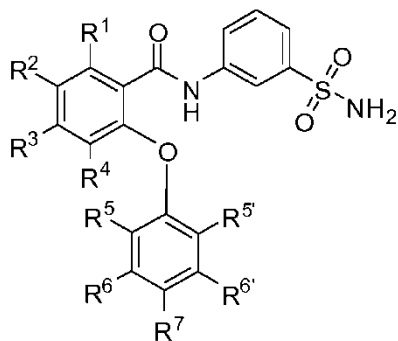
(19) NO
(51) Int Cl.
C07C 311/46 (2006.01)
A61K 31/18 (2006.01)

Norwegian Industrial Property Office

(21)	Translation Published	2018.03.05
(80)	Date of The European Patent Office Publication of the Granted Patent	2017.11.08
(86)	European Application Nr.	14748056.0
(86)	European Filing Date	2014.07.18
(87)	The European Application's Publication Date	2016.05.25
(30)	Priority	2013.07.19, US, 201361856146 P
(84)	Designated Contracting States:	AL ; AT ; BE ; BG ; CH ; CY ; CZ ; DE ; DK ; EE ; ES ; FI ; FR ; GB ; GR ; HR ; HU ; IE ; IS ; IT ; LI ; LT ; LU ; LV ; MC ; MK ; MT ; NL ; NO ; PL ; PT ; RO ; RS ; SE ; SI ; SK ; SM ; TR
	Designated Extension States:	BA; ME
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(54)	Title	SULFONAMIDES AS MODULATORS OF SODIUM CHANNELS
(56)	References Cited:	WO-A1-2012/177668, NIELSEN F E ET AL: "2-(4-Methoxyphenoxy)-5-nitro-N-(4-sulfamoylphenyl)benzamide activates Kir6.2/SUR1 KATP channels", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 14, no. 23, 6 December 2004 (2004-12-06), pages 5727-5730, XP004611108, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2004.09.057, US-A1- 2007 238 733

Enclosed is a translation of the patent claims in Norwegian. Please note that as per the Norwegian Patents Acts, section 66i the patent will receive protection in Norway only as far as there is agreement between the translation and the language of the application/patent granted at the EPO. In matters concerning the validity of the patent, language of the application/patent granted at the EPO will be used as the basis for the decision. The patent documents published by the EPO are available through Espacenet (<http://worldwide.espacenet.com>) or via the search engine on our website here: <https://search.patentstyret.no/>

Patentkrav1. Forbindelse med formel **I****I;**

eller et farmasøytisk akseptabelt salt derav,

5 hvor, uavhengig for hver forekomst:

R^1 er H, Cl, CH_3 , CF_3 eller syklopropyl;

R^2 er H, F, Cl, CN, CH_3 , CF_3 eller CHF_2 ;

R^3 er H, F, Cl, CN, CF_3 , OCF_3 eller CF_2CF_3 ;

R^4 er H;

10 R^5 er H, F, Cl, CH_3 , OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$ eller $OCHF_2$;

$R^{5'}$ er H, F, Cl, CH_3 , OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$ eller $OCHF_2$;

R^6 er H, F eller Cl;

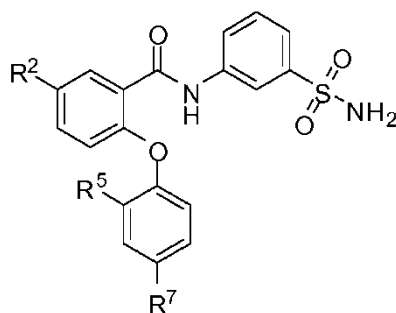
$R^{6'}$ er H, F eller Cl; og

R^7 er H, F, Cl, OCH_3 , OCF_3 , OCH_2CH_3 , $OCH(CH_3)_2$ eller $OCHF_2$,

15 forutsatt at R^1 , R^2 og R^3 ikke samtidig er hydrogen;

og at R^5 , $R^{5'}$, R^6 , $R^{6'}$ og R^7 ikke samtidig er hydrogen.

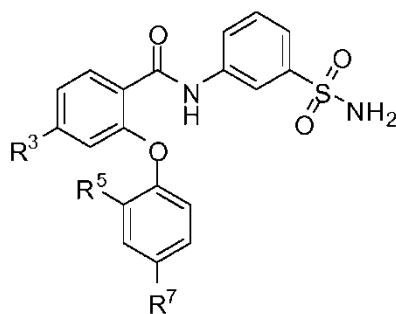
2. Forbindelse eller salt ifølge krav 1, hvor R^1 er H, CF_3 eller Cl, og/eller hvor R^1 er H eller CF_3 .
3. Forbindelse eller salt ifølge et hvilket som helst av kravene 1 til 2, hvor R^2 er H, CF_3 eller Cl, valgfritt hvor R^2 er H eller CF_3 .
- 5 4. Forbindelse eller salt ifølge et hvilket som helst av kravene 1 til 3, hvor R^3 er H, CF_3 , Cl eller OCF_3 , valgfritt hvor R^3 er H, CF_3 eller Cl.
5. Forbindelse eller salt ifølge et hvilket som helst av kravene 1 til 4, hvor R^5 er H, og/eller hvor R^6 eller $R^{6'}$ er H eller F, og/eller hvor R^7 er F, Cl, OCH_3 eller OCF_3 , valgfritt F eller OCH_3 .
- 10 6. Forbindelse eller salt ifølge krav 1, hvor forbindelsen har formel **I-D**:

**I-D,**

hvor, uavhengig for hver forekomst:

- R^2 er F, Cl, CN, CH_3 , CF_3 eller CHF_2 ;
- R^5 er F, Cl, CH_3 , OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$ eller $OCHF_2$; og
- 15 R^7 er F, Cl, OCH_3 , OCF_3 , OCH_2CH_3 , $OCH(CH_3)_2$ eller $OCHF_2$, valgfritt hvor R^2 er Cl eller CF_3 .
7. Forbindelse eller salt ifølge krav 6, hvor R^5 er F, Cl, CH_3 eller OCH_3 , og/eller hvor R^7 er F, Cl, OCH_3 eller OCF_3 .

8. Forbindelse eller salt ifølge krav 1, hvor forbindelsen har formel **I-E**:



I-E,

hvor, uafhængig for hver forekomst:

R^3 er F, Cl, CN, CF_3 , OCF_3 eller CF_2CF_3 ;

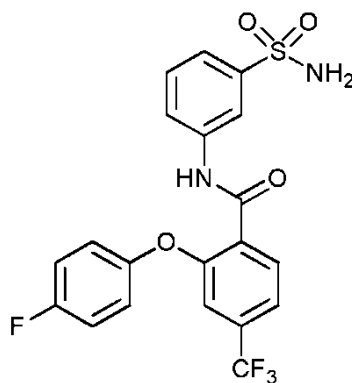
5 R^5 er F, Cl, CH_3 , OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$ eller $OCHF_2$; og

R^7 er F, Cl, OCH_3 , OCF_3 , OCH_2CH_3 , $OCH(CH_3)_2$ eller $OCHF_2$,

valgfritt hvor R^3 er Cl, CF_3 eller OCF_3 .

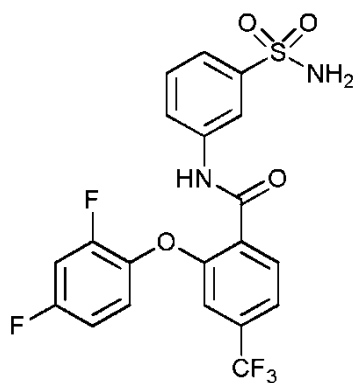
9. Forbindelse eller salt ifølge krav 8, hvor R^5 er F, Cl, CH_3 eller OCH_3 , og/eller hvor R^7 er F, Cl, OCH_3 eller OCF_3 .

10 10. Forbindelse eller salt ifølge krav 1, hvor forbindelsen eller saltet er valgt fra gruppen bestående av:

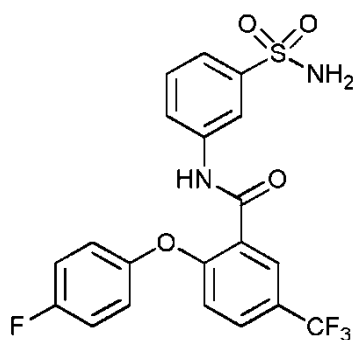


2-(4-fluorfenoksy)-N-(3-sulfamoylphenyl)-4-(trifluormetyl)benzamid;

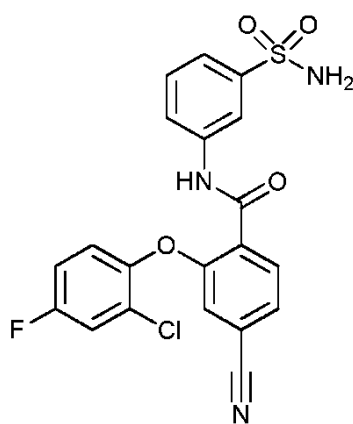
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2-(2,4-difluorfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;

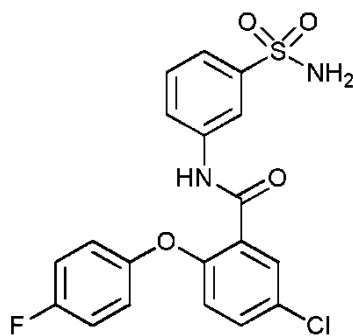


2-(4-fluorfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;



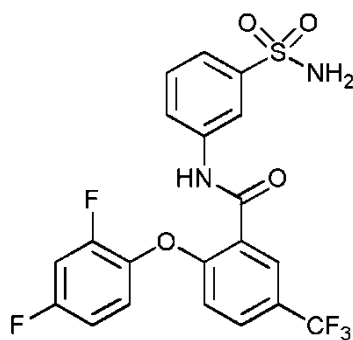
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2-(2-klor-4-fluorfenoksy)-4-cyano-N-(3-sulfamoylfenyl)benzamid;

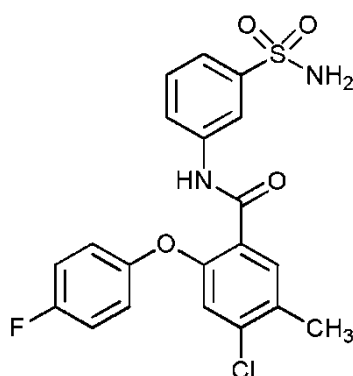


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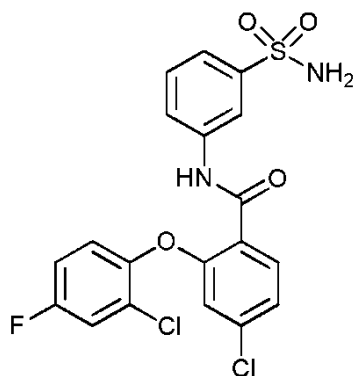
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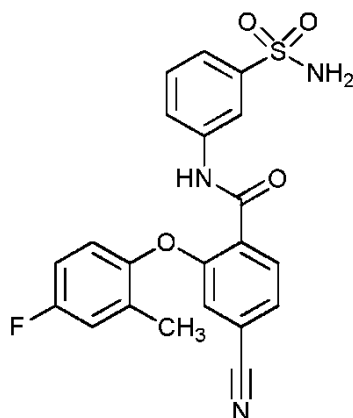
2-(2,4-difluorfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;



4-klor-2-(4-fluorfenoksy)-5-metyl-N-(3-sulfamoylfenyl)benzamid;



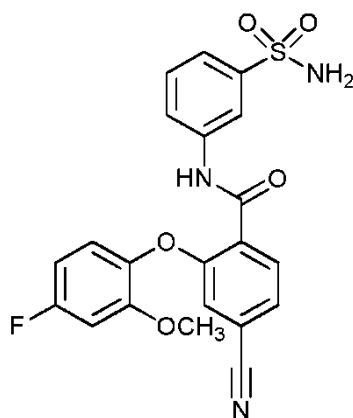
4-klor-2-(2-klor-4-fluorfenoksy)-N-(3-sulfamoylfenyl)benzamid;



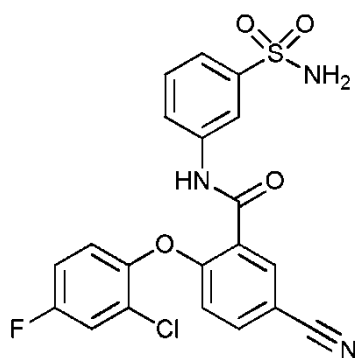
4-cyano-2-(4-fluor-2-metylfenoksy)-N-(3-sulfamoylfenyl)benzamid;

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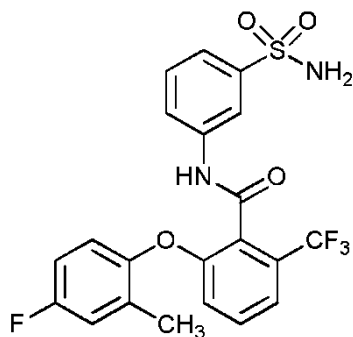
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4-cyano-2-(4-fluor-2-metoksyfenoksy)-N-(3-sulfamoylphenyl)benzamid;

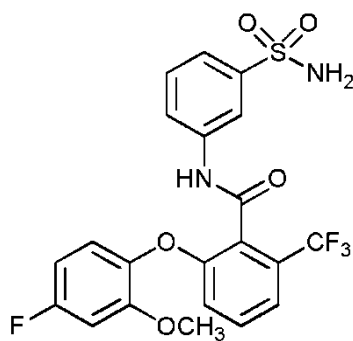


2-(2-klor-4-fluorfenoksy)-5-cyano-N-(3-sulfamoylphenyl)benzamid;



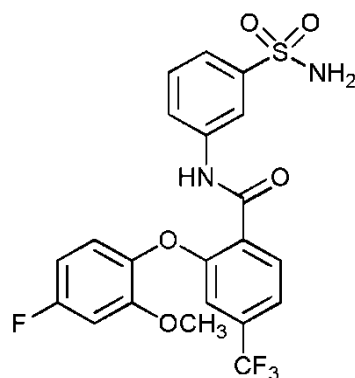
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2-(4-fluor-2-metylfenoksy)-N-(3-sulfamoylphenyl)-6-(trifluormetyl)benzamid;

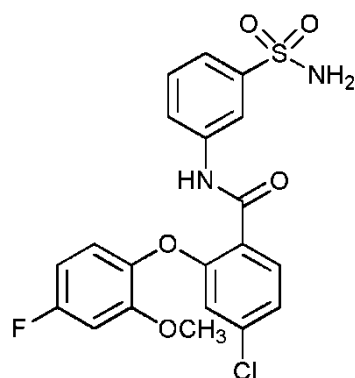


2-(4-fluor-2-metoksyfenoksy)-N-(3-sulfamoylphenyl)-6-(trifluormetyl)benzamid;

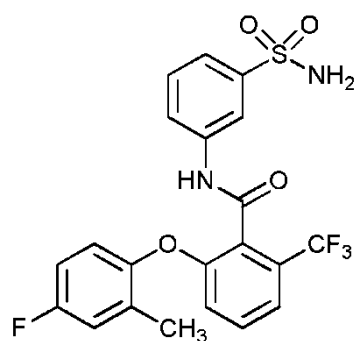
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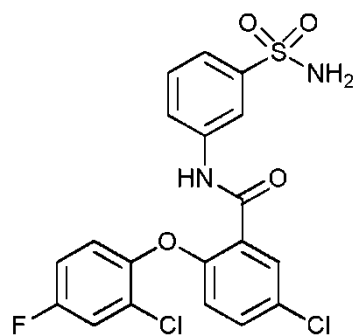
2-(4-fluor-2-metoksyfenoksi)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;



4-klor-2-(4-fluor-2-metoksyfenoksi)-N-(3-sulfamoylfenyl)benzamid;



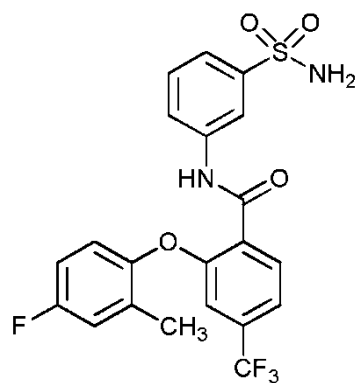
5-klor-2-(4-fluor-2-metoksyfenoksi)-N-(3-sulfamoylfenyl)benzamid;



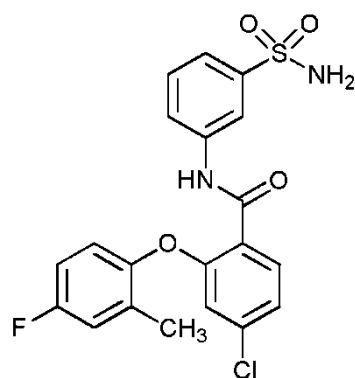
5-klor-2-(2-klor-4-fluorfenoksi)-N-(3-sulfamoylfenyl)benzamid;

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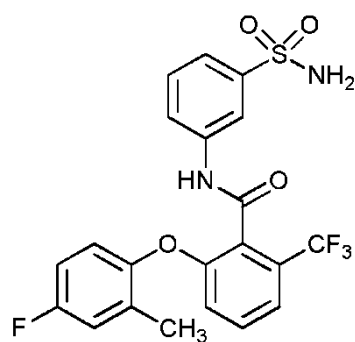
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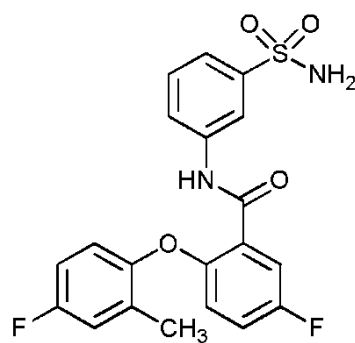
2-(4-fluor-2-metylfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;



4-klor-2-(4-fluor-2-metylfenoksy)-N-(3-sulfamoylfenyl)benzamid;

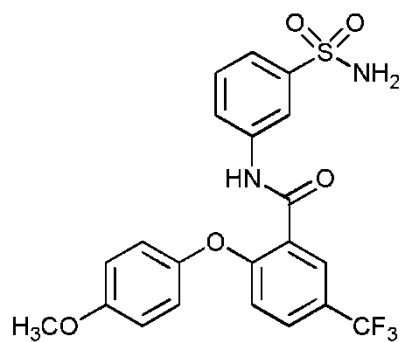


5-klor-2-(4-fluor-2-metylfenoksy)-N-(3-sulfamoylfenyl)benzamid;

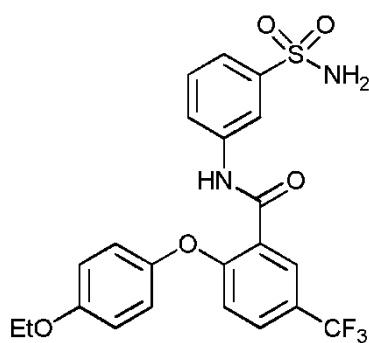


5-fluor-2-(4-fluor-2-metylfenoksy)-N-(3-sulfamoylfenyl)benzamid;

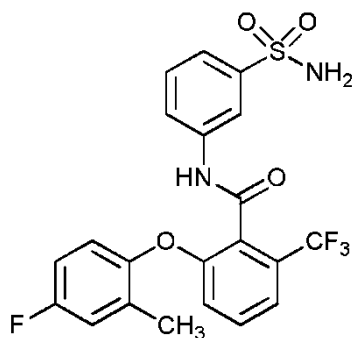
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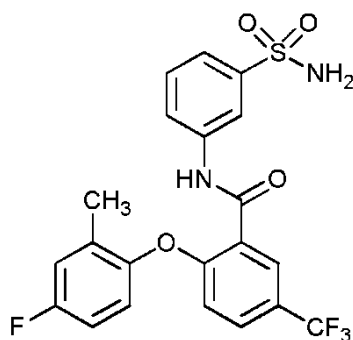
2-(4-metoksyfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;



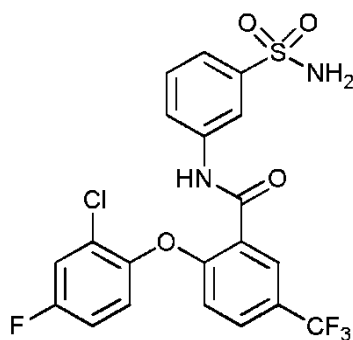
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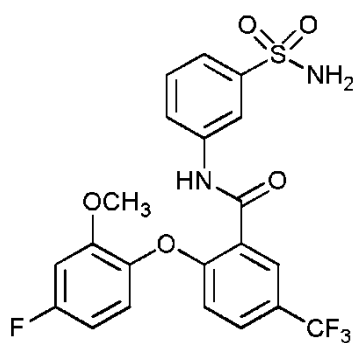
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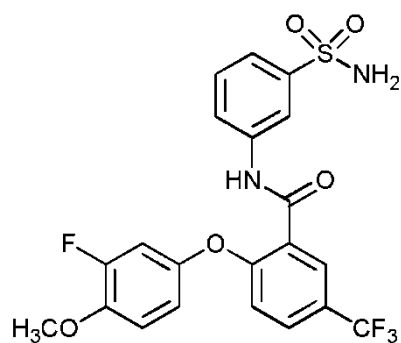
2-(4-fluor-2-metylfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;



2-(2-klor-4-fluorfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;

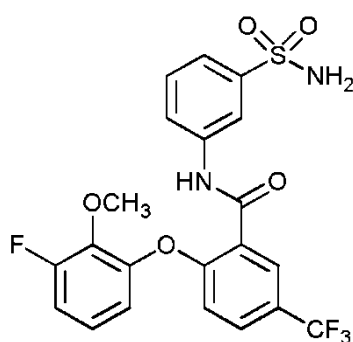


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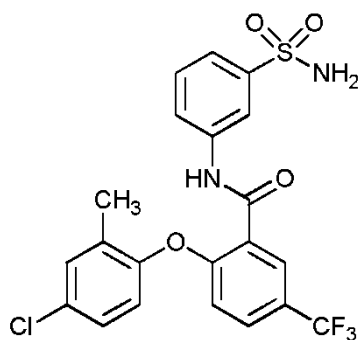


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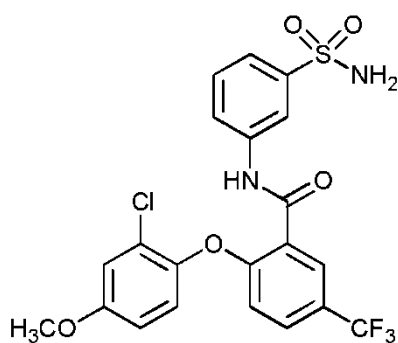
2-(3-fluor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;



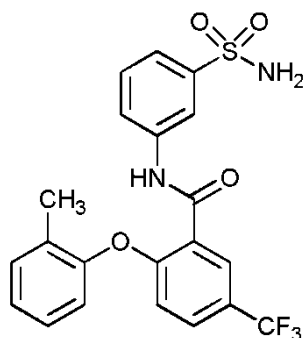
2-(3-fluor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;



2-(4-klor-2-metylfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;

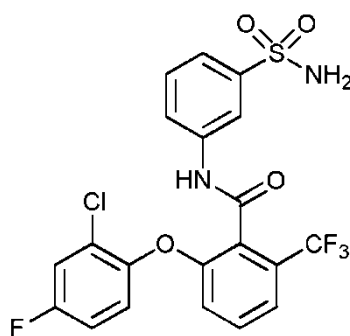


2-(2-klor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;

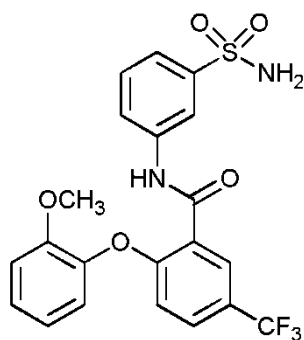


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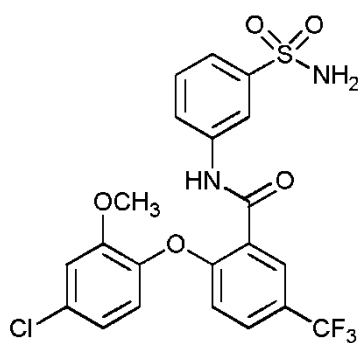
N-(3-sulfamoylfenyl)-2-(o-tolyl)oksy)-5-(trifluormetyl)benzamid;



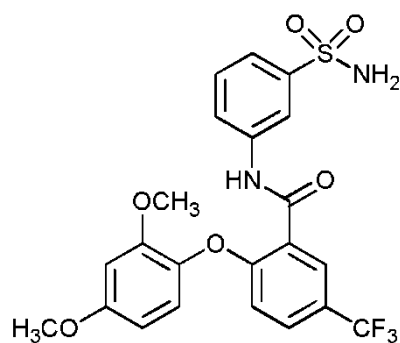
2-(2-klor-4-fluorfenoksy)-N-(3-sulfamoylfenyl)-6-(trifluormetyl)benzamid;



2-(2-metoksyfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;

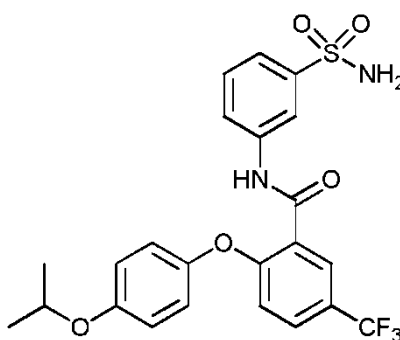


2-(4-klor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;

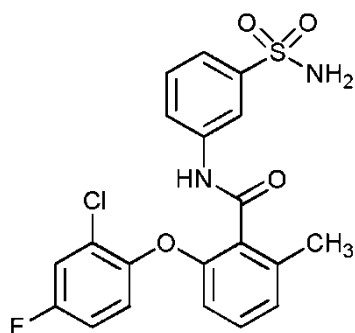


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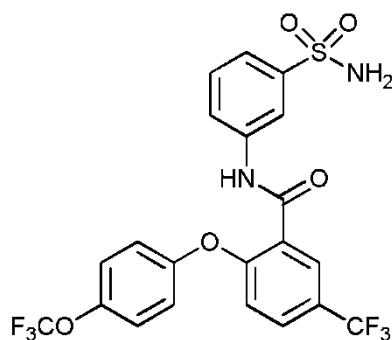
2-(2,4-dimetoksyfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;



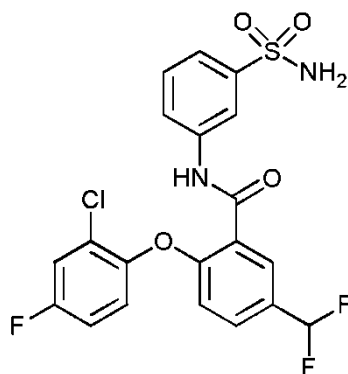
2-(4-isopropoksyfenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;



2-(2-klor-4-fluorfenoksy)-6-metyl-N-(3-sulfamoylfenyl)benzamid;

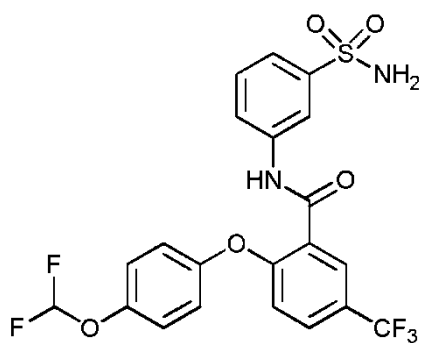


N-(3-sulfamoylfenyl)-2-(4-(trifluormetoksy)fenoksy)-5-(trifluormetyl)benzamid;

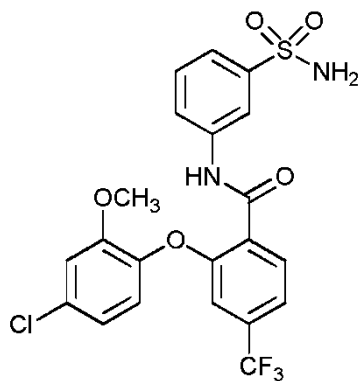


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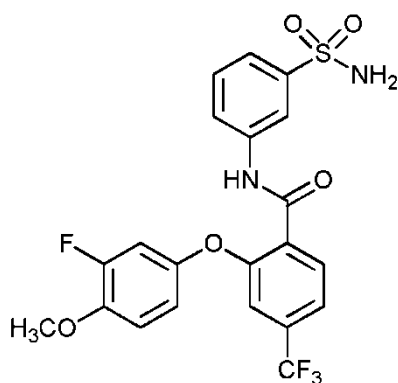
2-(2-klor-4-fluorfenoksy)-5-(difluormetyl)-N-(3-sulfamoylfenyl)benzamid;



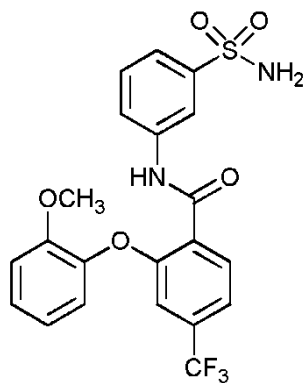
2-(4-(difluormetoksy)fenoksy)-N-(3-sulfamoylfenyl)-5-(trifluormetyl)benzamid;



2-(4-klor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;

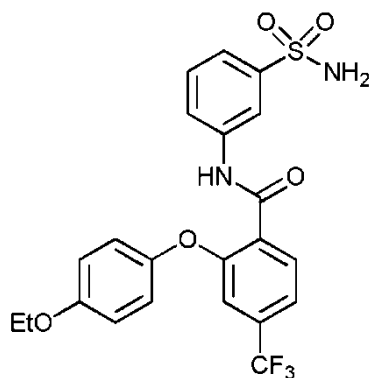


2-(3-fluor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;

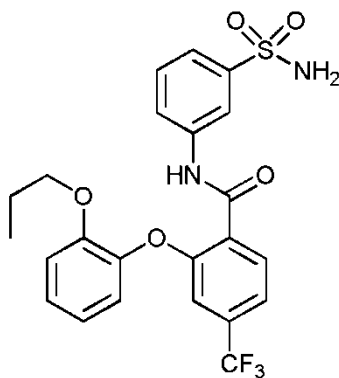


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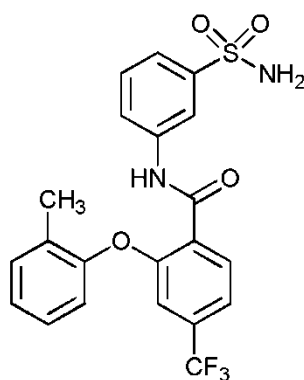
2-(2-metoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;



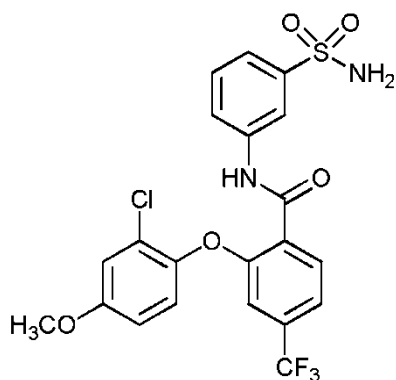
2-(4-etoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;



2-(2-propoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;

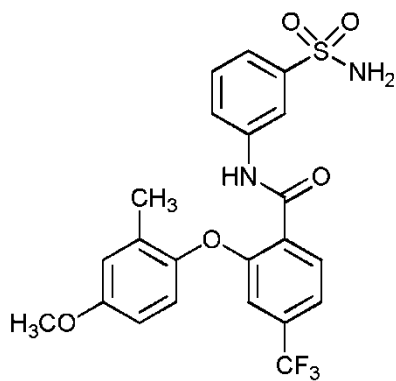


N-(3-sulfamoylfenyl)-2-(o-tolyloksy)-4-(trifluormetyl)benzamid;

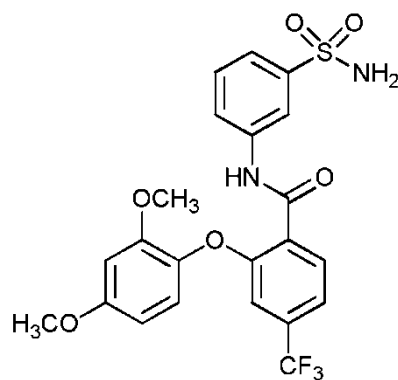


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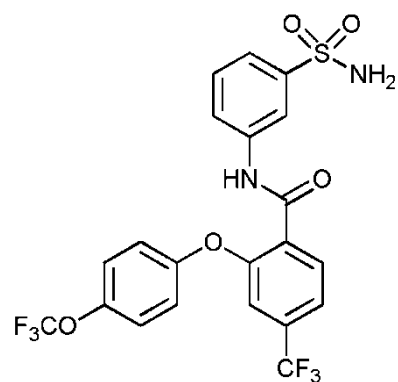
2-(2-klor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;



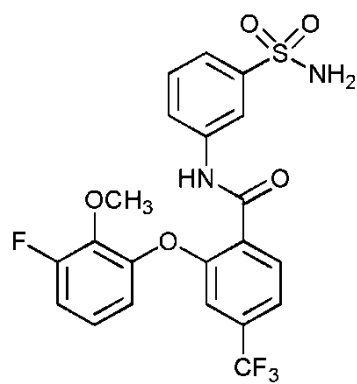
2-(4-metoksy-2-metylfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;



2-(2,4-dimetoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;

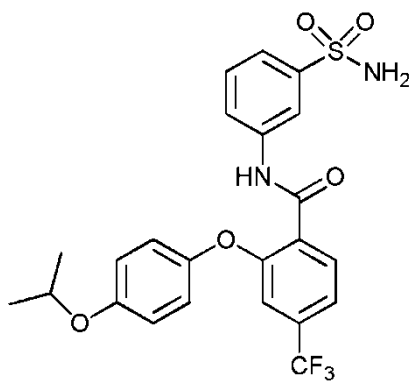


N-(3-sulfamoylfenyl)-2-(4-(trifluormetoksy)fenoksy)-4-(trifluormetyl)benzamid;

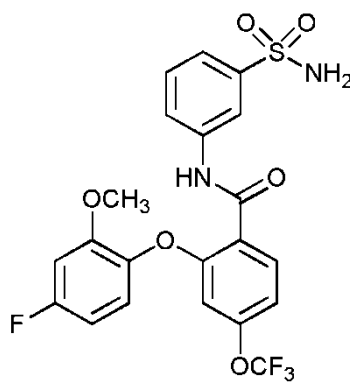


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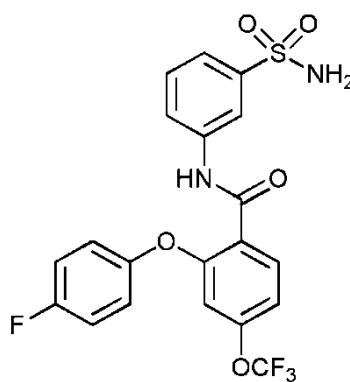
2-(3-fluor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;



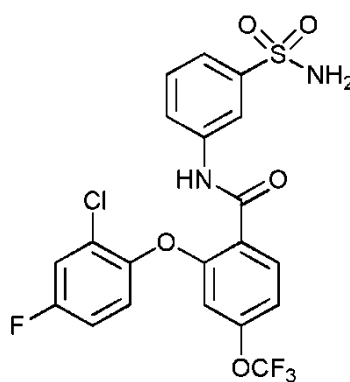
2-(4-isopropoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;



2-(4-fluor-2-metoksyfenoksy)-N-(3-sulfamoylphenyl)-4-(trifluormetoksy)benzamid;

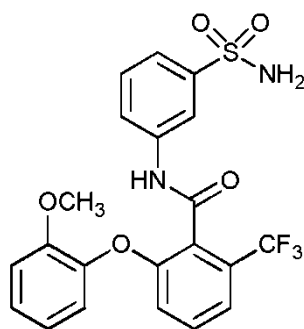


2-(4-fluorfenoksy)-N-(3-sulfamoylphenyl)-4-(trifluormetoksy)benzamid;

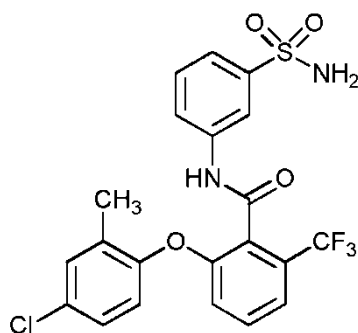


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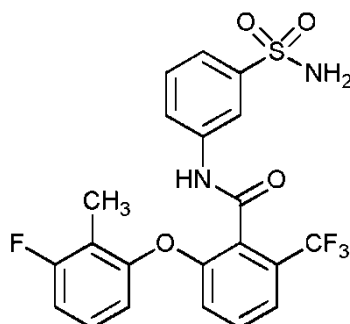
2-(2-klor-4-fluorfenoksy)-N-(3-sulfamoylphenyl)-4-(trifluormetoksy)benzamid;



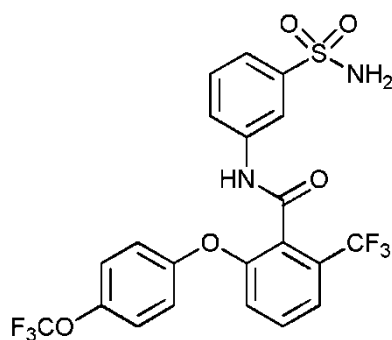
2-(2-metoksyfenoksy)-N-(3-sulfamoylphenyl)-6-(trifluormetyl)benzamid;



2-(4-klor-2-metylfenoksy)-N-(3-sulfamoylfenyl)-6-(trifluormetyl)benzamid;

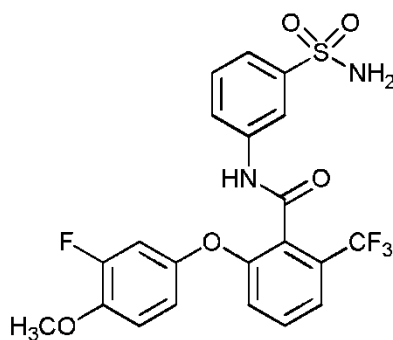


2-(3-fluor-2-metylfenoksy)-N-(3-sulfamoylfenyl)-6-(trifluormetyl)benzamid;

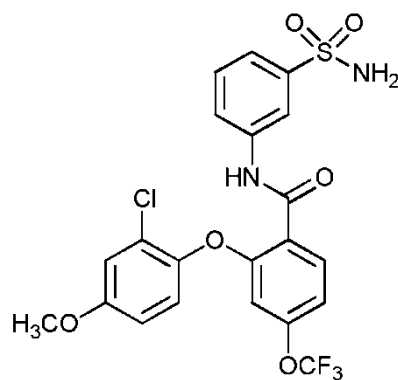


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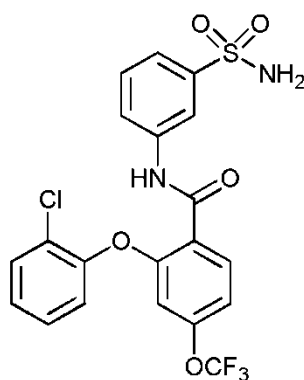
N-(3-sulfamoylfenyl)-2-(4-(trifluormetoksy)fenoksy)-6-(trifluormetyl)benzamid;



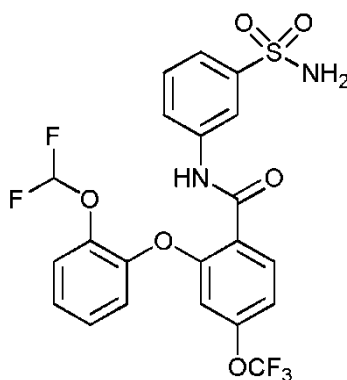
2-(3-fluor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)-6-(trifluormetyl)benzamid;



2-(2-klor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetoksy)benzamid;

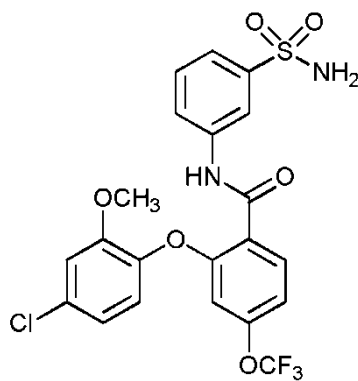


2-(2-klorfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetoksy)benzamid;

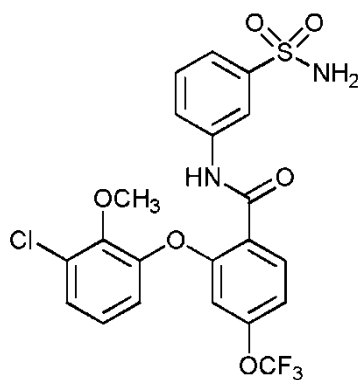


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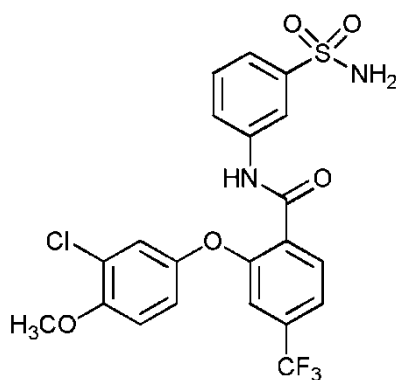
2-(2-(difluormetoksy)fenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetoksy)benzamid;



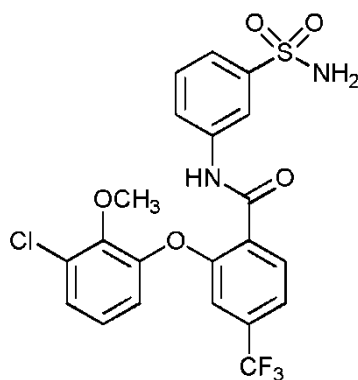
2-(4-klor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetoksy)benzamid;



2-(3-klor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetoksy)benzamid;

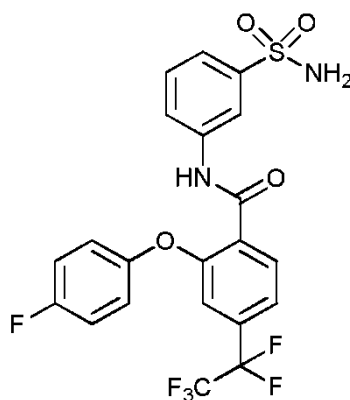


2-(3-klor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;

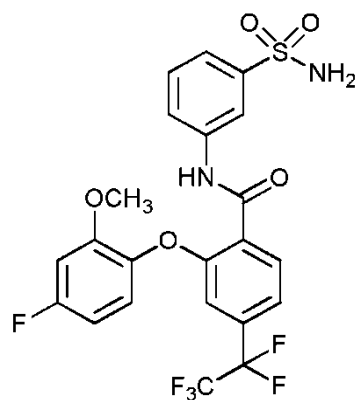


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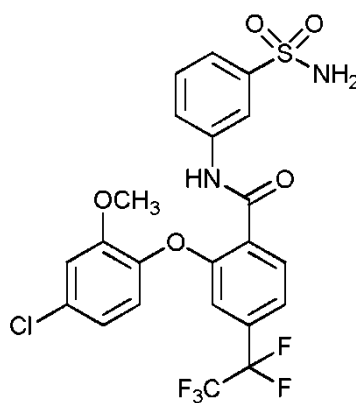
2-(3-klor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;



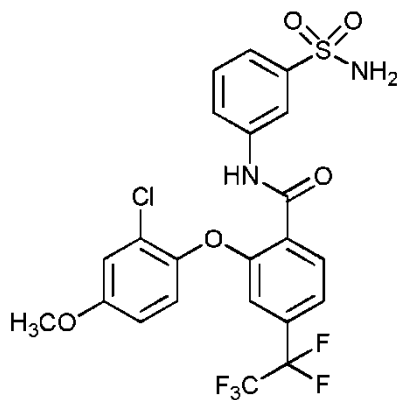
2-(4-fluorfenoksy)-4-(perfluoretyl)-N-(3-sulfamoylfenyl)benzamid;



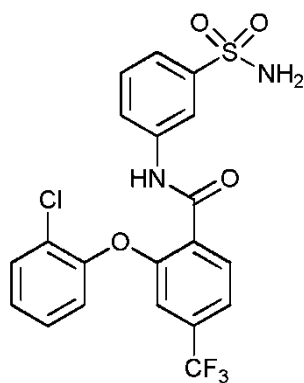
2-(4-fluor-2-metoksyfenoksy)-4-(perfluoretyl)-N-(3-sulfamoylphenyl)benzamid;



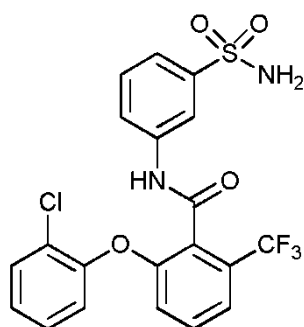
2-(4-klor-2-metoksyfenoksy)-4-(perfluoretyl)-N-(3-sulfamoylphenyl)benzamid;



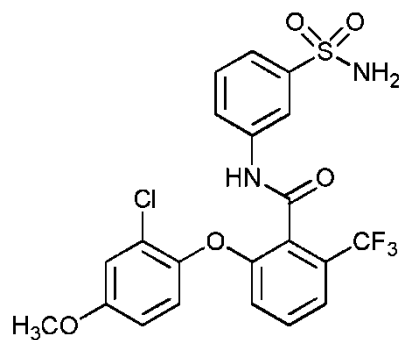
2-(2-klor-4-metoksyfenoksy)-4-(perfluoretyl)-N-(3-sulfamoylphenyl)benzamid;



2-(2-klorfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)benzamid;

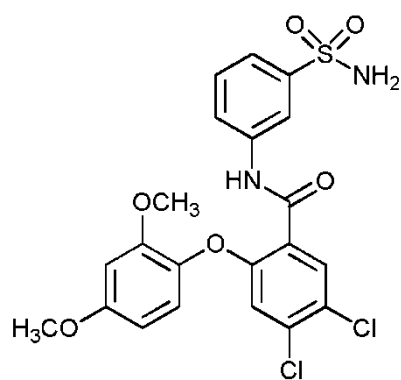


2-(2-klorfenoksy)-N-(3-sulfamoylfenyl)-6-(trifluormetyl)benzamid;

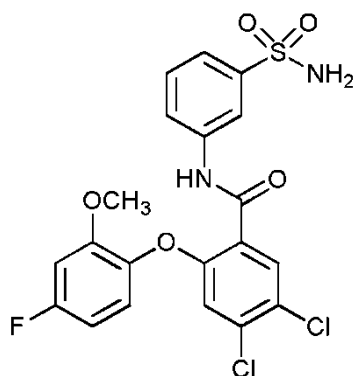


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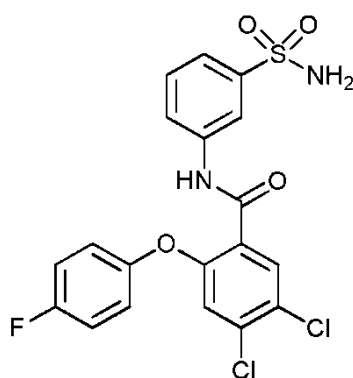
2-(2-klor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)-6-(trifluormetyl)benzamid;



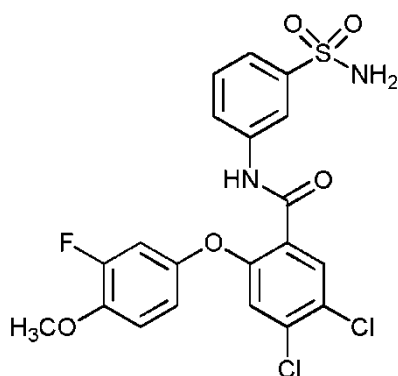
4,5-diklor-2-(2,4-dimetoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;



4,5-diklor-2-(4-fluor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;

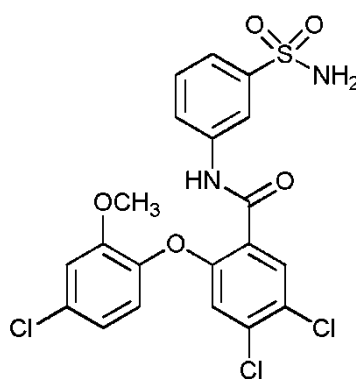


4,5-diklor-2-(4-fluorfenoksy)-N-(3-sulfamoylfenyl)benzamid;

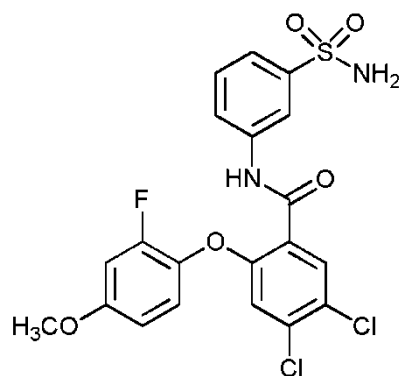


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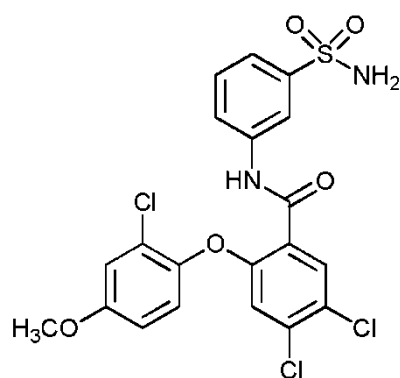
4,5-diklor-2-(3-fluor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;



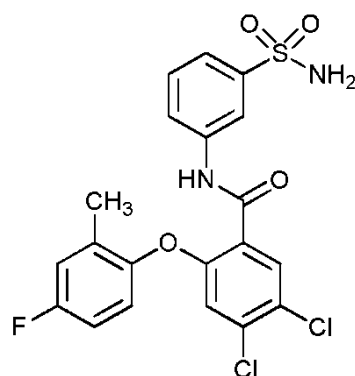
4,5-diklor-2-(4-klor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;



4,5-diklor-2-(2-fluor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;

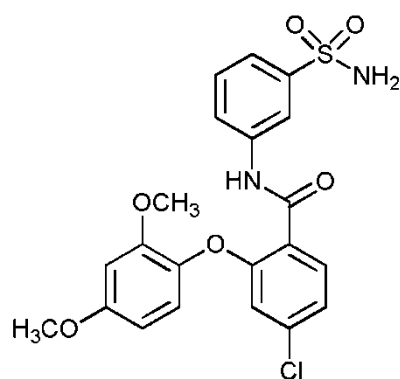


4,5-diklor-2-(2-klor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;

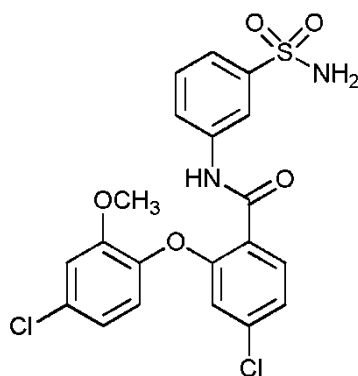


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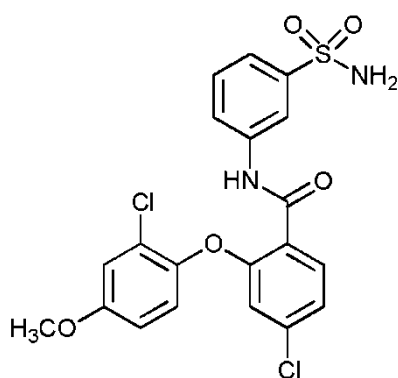
4,5-diklor-2-(4-fluor-2-metylfenoksy)-N-(3-sulfamoylfenyl)benzamid;



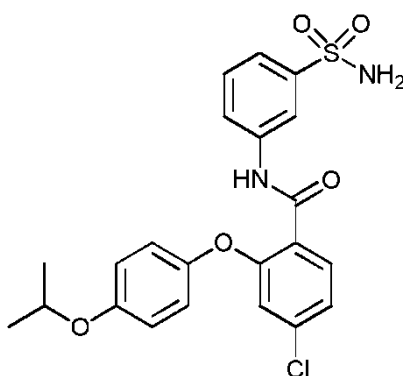
4-klor-2-(2,4-dimetoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;



4-klor-2-(4-klor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;

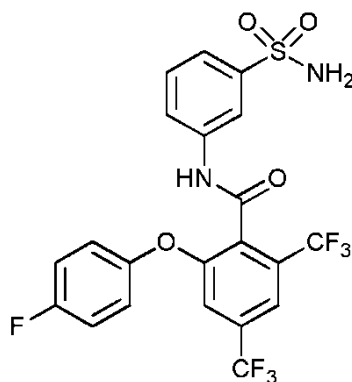


4-klor-2-(2-klor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;

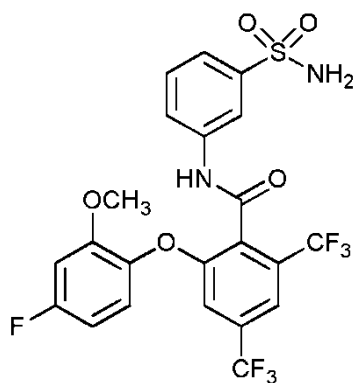


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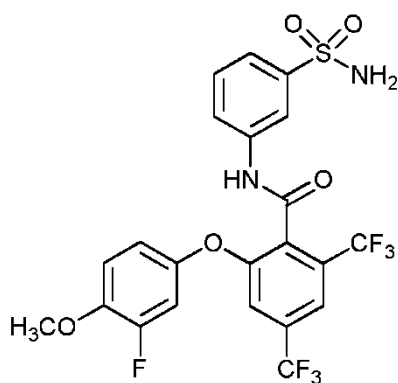
4-klor-2-(4-isopropoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;



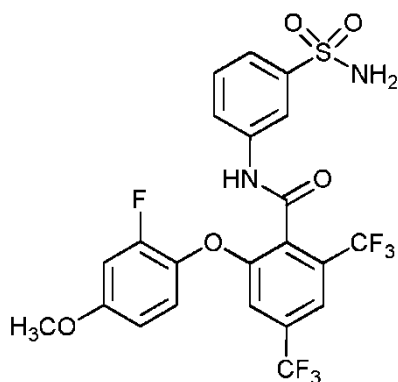
2-(4-fluorfenoksy)-N-(3-sulfamoylfenyl)-4,6-bis(trifluormetyl)benzamid;



2-(4-fluor-2-metoksyfenoksy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluormetyl)benzamid;

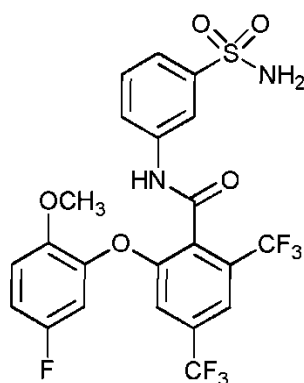


2-(3-fluor-4-metoksyfenoksy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluormetyl)benzamid;

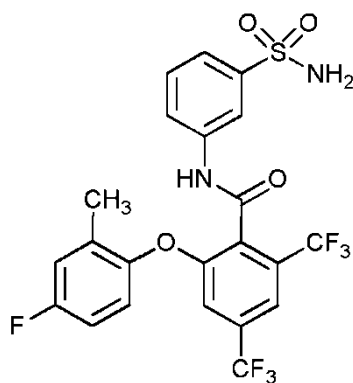


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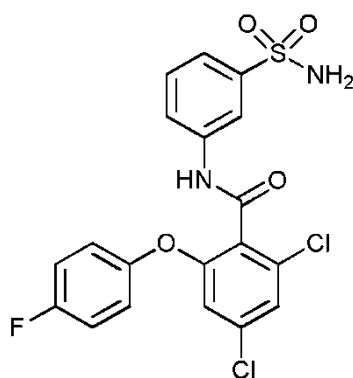
2-(2-fluor-4-metoksyfenoksy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluormetyl)benzamid;



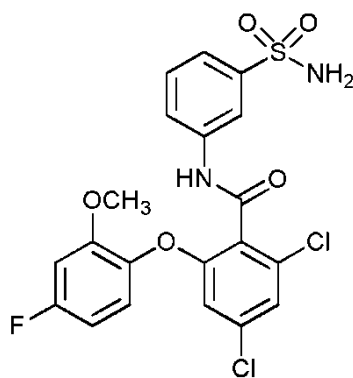
2-(5-fluor-2-metoksyfenoksy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluormetyl)benzamid;



2-(4-fluor-2-metylfenoksy)-N-(3-sulfamoylfenyl)-4,6-bis(trifluormetyl)benzamid;

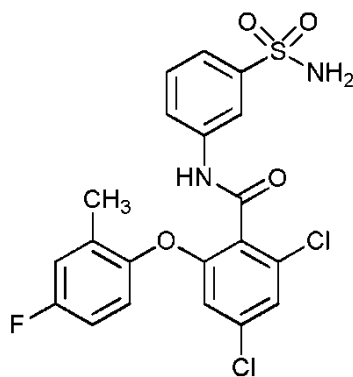


2,4-diklor-6-(4-fluorfenoksy)-N-(3-sulfamoylfenyl)benzamid;

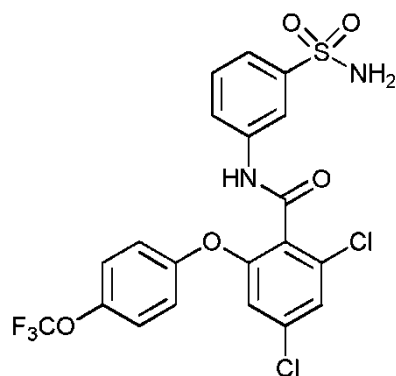


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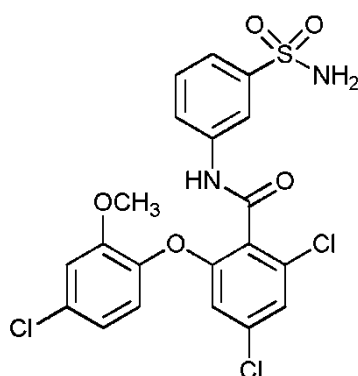
2,4-diklor-6-(4-fluor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;



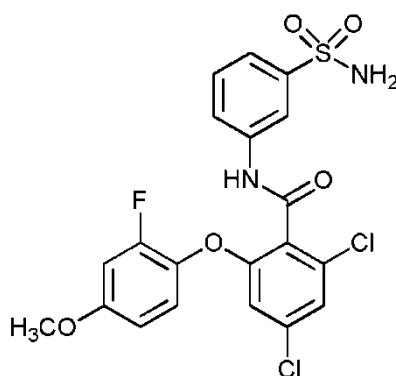
2,4-diklor-6-(4-fluor-2-metylfenoksy)-N-(3-sulfamoylfenyl)benzamid;



2,4-diklor-N-(3-sulfamoylfenyl)-6-(4-(trifluormetoksy)fenoksy)benzamid;

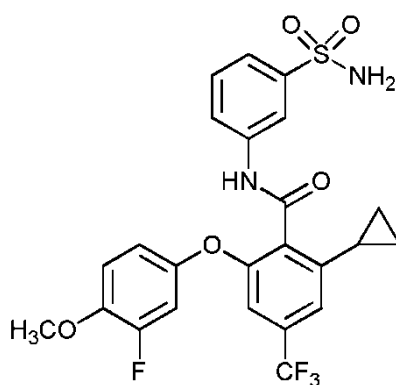


2,4-diklor-6-(4-klor-2-metoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid;



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2,4-diklor-6-(2-fluor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)benzamid; og



2-cyklopropyl-6-(3-fluor-4-metoksyfenoksy)-N-(3-sulfamoylfenyl)-4-(trifluormetyl)-benzamid;

eller et farmasøytisk akseptabelt salt derav.

11. Farmasøytisk sammensetning omfattende en forbindelse eller et farmasøytisk akseptabelt salt derav ifølge et hvilket som helst av kravene 1 til 10 og én eller flere farmasøytisk akseptable bærere eller vehikler.

5 12. Farmasøytisk sammensetning ifølge krav 11, hvor forbindelsen eller det farmasøytisk akseptable salt derav foreligger i en terapeutisk virksom mengde.

13. Forbindelse eller et farmasøytisk akseptabelt salt ifølge et hvilket som helst av kravene 1 til 10, eller en farmasøytisk sammensetning ifølge krav 11 eller 12, for anvendelse i en fremgangsmåte for å hemme en spenningsstyrt natriumkanal i
10 et individ, valgfritt hvor den spenningsstyrte natriumkanal er Nav1.8.

14. Forbindelse eller et farmasøytisk akseptabelt salt derav ifølge et hvilket som helst av kravene 1 til 10, eller en farmasøytisk sammensetning ifølge krav 11 eller 12, for anvendelse i en fremgangsmåte for å behandle eller redusere alvoret i et individ av kroniske smerter, magesmerter, neuropatiske smerter,
15 muskelskjelettsmerter, akutte smerter, inflammatorisk smerte, kreftsmarter, idiopatiske smerter, multippel sklerose, Charcot-Marie-Tooth-syndrom, inkontinens eller hjertearytmi, valgfritt:

(i) for anvendelse i en fremgangsmåte for å behandle eller redusere alvoret i et individ av magesmerter, hvor magesmertene omfatter smerter ved inflammatorisk
20 tarmsykdom, smerter ved Crohns sykdom eller smerter ved interstitial cystitt,

(ii) for anvendelse i en fremgangsmåte for å behandle eller redusere alvoret i et individ av neuropatiske smerter, hvor de neuropatiske smerter omfatter post-herpetisk neuralgi, diabetisk neuralgi, smertefull HIV-forbundet sensorisk neuropati, trigeminal neuralgi, brennende munnsyndrom, post-
25 amputasjonssmerter, fantomsmerter, smertefullt neuroma; traumatisk neuroma; Mortons neuroma; nerveklemskader, spinal stenose, karpaltunnelsyndrom, radikulær smerte, isjassmerter; nerveavulsjonsskade, brachial plexus avulsjonsskade; komplekst regionalt smertesyndrom, legemiddelterapi-indusert neuralgi, kreft-kjemoterapi-indusert neuralgi, anti-retroviral terapi-indusert
30 neuralgi; smerter etter ryggmargsskade, idiopatisk små-fibret neuropati, idiopatisk sensorisk neuropati eller trigeminal autonom cefalalgi,

(iii) for anvendelse i en fremgangsmåte for å behandle eller redusere alvoret i et individ av muskelskjelettsmerter, hvor muskelskjelettsmertene omfatter osteoartrittsmerter, ryggsmarter, forkjølelsessmerter, forbrenningssmerter eller tannpine, valgfritt osteoartrittsmerter,

- 5 (iv) for anvendelse i en fremgangsmåte for å behandle eller redusere alvoret i et individ av inflammatoriske smerter, hvor de inflammatoriske smerter omfatter reumatoid artritt-smerter eller vulvodynia, eller

(v) for anvendelse i en fremgangsmåte for å behandle eller redusere alvoret i et individ av idiopatiske smerter, hvor de idiopatiske smerter omfatter

- 10 fibromyalgismerter.

15. Forbindelse eller et farmasøytisk akseptabelt salt eller en farmasøytisk sammensetning for anvendelse ifølge et hvilket som helst av kravene 13 til 14, hvor individet behandles med ett eller flere ytterligere terapeutiske midler som administreres samtidig med, før eller etter behandlingen med forbindelsen, saltet

- 15 eller den farmasøytiske sammensetning.