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SYNTHESIS OF NOVEL FLUORINATED N-(PHENYL)-2-(3-MORPHOLIN-4-YL-PHENOXY)-ACETAMIDE DERIVATIVES AND EVALUATION OF ITS ANTIMICROBIAL ACTIVITY

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Abstract: A series of fluorinated N-(phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide derivatives were synthesized using ionic liquid as solvent and base, All the synthesized compounds were tested for their antibacterial activities. all fluorinated derivatives exhibited antibacterial activity against the microorganisms tested. Compounds with trifluoromethyl group shown excellent activity

***Index Terms*:** N-(phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide, ionic liquid, antibacterial activities.

I.INTRODUCTION

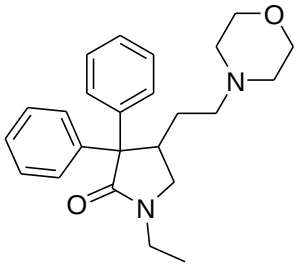
Currently huge number of diseases are spreading all over the world and in order to treat these diseases there is need to search for new drugs that have added advantageous properties over existing drugs present in market. In this study we have made an attempt to search some novel drug moieties by synthesizing them and checking its antibacterial activity. Firstly for designing novel moieties we have decided to incorporate heterocyclic moieties due to their binding properties and diverse biological properties. After intense literature we have decided Morpholine ring as it satisfies our interest.

Morpholine (tetrahydro-1,4-oxazine) is a heterocycle having chemical formula $O(CH_2CH_2)_2NH$ that is widely exploited in medicinal chemistry due to its advantageous physicochemical, biological, and metabolic properties as well as its mostly facile synthetic routes[1,2] Preludin was the first morpholine-containing drug used for obesity[3]. In 1957 a series of morpholine containing compounds were developed as potent analgesic agents[4], Morpholine is mostly used as a simple base or as a N-alkylating agent due to this fact it is much less explored moiety than other Heterocycles[5,6,7]. This could lead an advantage as a compound class that may have important applications in the ongoing search for new pharmaceutically active compounds. The substituted morpholines have long been known to possess a wide range of biological actions ranging from analgesic, anti-inflammatory, antioxidant, ant obesity, and antihyperlipidemic to antimicrobial, ant neurodegenerative and anticancer activity [8-12].

The acetamide is an organic compound with the formula CH_3CONH_2, its derivatives are obtained by simple and rapid chemical synthesis, had interesting biological activities such as *in vitro* anti-inflammatory and antioxidant activities. They are used as a solvent for many organic and inorganic compounds. Also used in explosives, plasticizer, hygroscopic agent, Stabilizer, penetrating agent, fire suppressant [13,14]. The Acetazolamide is prescribed to treat excess fluid accumulation due to congestive heart failure. It is also used to treat glaucoma or increased pressure in the eye, seizures or epilepsy, mountain sickness, periodic paralysis, or muscle weakness, and to reduce the increased pressure in areas surrounding the brain and spinal cord [15].

The introduction of the fluorine atom in a drug/drug-like molecule results in a significant influence on its biological and physical properties due to enhancement of membrane permeability, hydrophobic bonding, stability against metabolic oxidation, etc. [16]. Fluorine is known as 'bioisostere' of the H and OH. Fluorine is more electronegative than hydrogen, but it has the same atomic radius that of hydrogen hence H-atom can be replaced by F-atom. Insertion of fluorine atoms in a potential drug molecule can have dramatic effects on the properties of that molecule such as making them more selective, increasing their efficacy, making them easier to administer, etc[17,18].

Currently there is need for identification of small potent compounds that selectively bind to the target of interest with high affinity,also the benefit of synthesizing small is that while interacting with large proteins moieties the large ligands face binding issue and can't fit in the pocket sites of proteins [19,20]. Due to this synthesizing small ligand makes protein-ligand interaction efficient. So by observing these factors we have decided to synthesize small acetamide substituted fluorinated morpholine derivatives.



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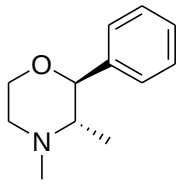

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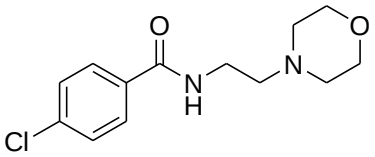
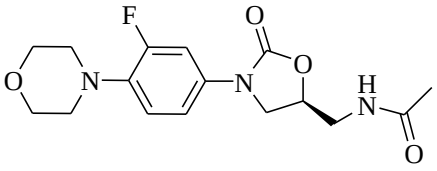
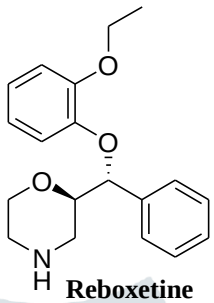


Moclobemide

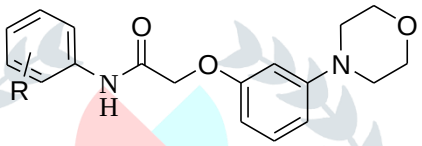


Linezolide



Reboxetine

Fig.1 Fluorine containing Antibiotics



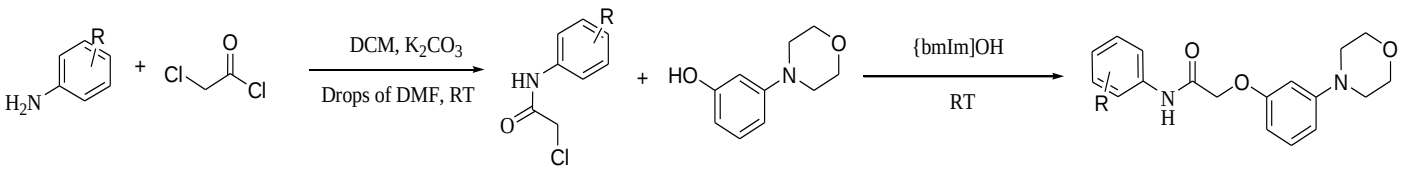
3 a-m

Fig. 2 Synthesized Fluorinated Morpholine

II. RESULTS AND DISCUSSION:

2.1 Chemistry:

The Designed synthetic route initiated with 2,4-Difluoro-aniline **1** was reacted with chloroacetyl chloride and potassium carbonate in dichloromethane at R.T to afford the 2-Chloro-N-(2,4-difluoro-phenyl)-acetamide **2** The formation of product was confirmed by the mass spectroscopy it shows m/z at 205.5 for [M^+ +1], 2-Chloro-N-(2,4-difluoro-phenyl)-acetamide **2** was treated with 3-morpholinophenol by 2 methods 1. Conventional method by using base and solvent and 2. Using ionic liquid as a solvent and base gave the desired product in 70-75 and 80-90 % yield respectively to get N-(2,4-Difluoro-phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide



1 **2** **3 a-m**

Fig. 3 Scheme

Charectrization of compound N-(2,4-Difluoro-phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide **3**a was carried out using 1H NMR, compound **3a** exhibited a triplet at 3.12 ppm with Coupling constant 4.8 Hz for 4 protons of N-CH2 protons of morpholine ring and corresponding OCH2 protons resonated at at 3.98 ppm with coupling constant 4.8 Hz for 4 protons .Aromatic ring protons of difluorophenyl ring exhibited signals at 7.11-7.15 (m, 2H), 7.36-7.43 (t, J = 4.8 Hz 1H) , 3-morpholino phenol ring protons resonated at 7.18(t, J=8.0Hz, 1H), 6.55(dd, J=2.4,8.4Hz, 1H), 6.43(t, J=2.0Hz, 1H), 6.40 (dd, J=2.0, 7.6Hz, 1H). 19F NMR spectrum exhibited signals at -115.5(1F),-120.7 (1F), MS (m/z): 349.2 [M+ +1]. All the spectral values are in agreement wth the gross structure of synthesized compound.

Condensation of 3-morpholinophenol with 2-Chloro-N-(2,4-difluoro-phenyl)-acetamide using Potassium carbonate as base and DMF as solvent at 65^0C afforded N-(2,4-Difluoro-phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide **(3a)** in 70-80 %yields, in this reaction work-up of reaction is difficult due to formation of emulsion in reaction. We tried this reaction by using task specific ionic liquid as solvent and base for reaction . All the compounds formed in 80-90 % yields which is better than the conventional method using DMF as solvent and heating ,during heating of reactions reaction yield decreases due to formation of impurities /emulsions and longer reaction time than using ionic liquid.

Table-1 Condensation of 3-morpholino-phenol with Various 2-Chloro-N-(-phenyl)-acetamide

No.	Aniline	Comp	[BmIm]OH		Conventional using K_2CO_3 ,DMF	
			Yield(%)	Time(min)	Yield(%)	Time(hr)
1	2,4-Difluoro-aniline	**3a**	82	30	71	8
2	2,6-Difluoro-aniline	**3b**	85	30	69	9
3	3,4-Difluoro-aniline	**3c**	88	30	74	9
4	3,5-Difluoro-aniline	**3d**	90	30	75	6
5	2,4,5-Trifluoro-aniline	**3e**	86	40	77	10
6	2,4-Difluoro-benzylamine	**3f**	82	40	73	10
7	3-Chloro-4-fluoro-aniline	**3g**	82	40	73	10
8	2-Trifluoromethyl-aniline	**3h**	80	20	71	5
9	3-Trifluoromethyl-aniline	**3i**	85	40	75	9
10	4-Trifluoromethyl-aniline	**3j**	78	20	74	4
11	4-Trifluoromethoxy-aniline	**3k**	74	20	68	4
12	3,5-Dichloro-4-(1,1,2,2-tetrafluoro-ethoxy)-aniline	**3l**	80	20	71	4
13	4-Fluoro-aniline	**3m**	81	25	73	8

2.2 Invitro antibacterial activity:

The newly synthesized compounds were tested to evaluate their antibacterial and antifungal activity. All these compounds were found to exhibit good antibacterial and antifungal activity against different species of bacteria and fungi. From the activity data (**Table 2**). Compound **3a, 3b, 3c, 3f, 3g,3k** showed good activity against all bacteria. Compound **3b, 3c, 3g, 3k** showed good activity against fungi. Among all tested bacteria and fungi compound **3c, 3g, 3k** showed excellent activity against *staphylococcus aureus, Bacillus subtillis* and *Escherichia coli*. Among the other compounds **3d, 3h, 3i, 3j, 3m, 3n** showed good activity against all the bacteria. Compounds **3d, 3h,** and **3m** showed good activity against *Aspergillus Niger* and *Rhizopus Ostoyae* fungi. Among all the compounds **3b, 3g, 3k** were found to be most active compounds.

- S.A.- *Staphylococus aureus*, B.S.- *Bacillus subtilis*, E.C.- *Escherichia coli*, A.N. *Aspergillius Niger*, R. O.- *Rhizopus Ostoyae.*
- These results are average results of four experiments.
- These compounds were used at concentration of 100 µg/mL.
- Streptomycin for bacteria and Nystain for fungi were used as standard at concentration of 30 µg.

. **Table2** Antimicrobial activity of N-(phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide

Comp. No. 3	Zone of Inhibition (mm)				
	Bacteria			Fungi	
	S. A. *NCLM No.2602*	***B. S.*** *NCLM No.2458*	***E. C.*** *NCLM No.2809*	***A. N.*** *NCLM No.617*	***R.O.*** *NCLM No.1299*
a	7.1	6.8	7.3	8.0	5.9
b	8.1	8.0	7.1	7.1	7.1
c	11.3	10.5	9.9	8.8	7.5
d	7.6	7.2	6.3	5.9	6.3
e	5.7	6.1	5.4	6.1	4.9
f	9.2	8.1	7.4	6.7	5.9

g	9.13	8.4	7.21	6.19	6.2
h	6.4	6.3	6.9	5.5	5.0
i	8.4	7.9	7.3	5.9	5.2
j	6.5	5.9	5.5	6.1	4.9
k	10.7	9.9	9.7	8.3	7.13
l	9.0	8.8	7.41	8.0	6.5
m	8.8	8.0	8.7	8.0	5.4
Standard	12	10	11	10	9

III. CONCLUSION

In summary, we have synthesized a novel of N-(phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide derivatives by conventional knoenvengel reaction and by using ionic liquid and product of aromatic anilines and chloroacetylchloride , by using task specific ionic liquid got the excellent yields and reduce the time of reaction drastically than the normal substitution reaction in DMF Compounds having CF_3 trifluoromethyl group on aromatic aniline moiety showed excellent activity against tested bacterial and fungi strains. MIC of the all tested compounds shows moderate activity.

IV. EXPERIMENTAL

4.1 Method

Progress of reaction was monitored by silica gel-G coated TLC plates in Ethyl acetate: Hexane system (5:5). The spot was visualized by exposing dry plate in iodine vapors. Melting points were determined by the melting point determination apparatus (Buchi-M565) in open capillary tubes. Infrared spectra were recorded on Agilent spectrophotometer (ƛmax in cm^{-1}). 1H, 19FNMR spectra were recorded on Bruker Advance III 300 NMR Ultra Shield Spectrometer using $CDCl_3$ as a solvent and tetramethyl silane as internal standard. Chemical shift value is expressed in delta parts per million (ppm). The antimicrobial activity of the compounds was assayed by antimicrobial susceptibility test[21] 100 µl of 24-hour growth of each microorganism was spread on the surface of nutrient agar for bacteria (Mac Conkey's agar for *E.coli*) and potato dextrose agar for fungi, in Petri plates. (Composition of media is given below). 50µl compounds at the concentration of 100 µg /ml in DMSO saturated on discs of 6mm diameter were kept on agar surface. The plates were refrigerated for 2 hours to allow pre-diffusion of the compounds from the discs into the seeded agar layer and then incubated at 37 ºC for 24 hours for bacteria and 28 ºC for 48 hours for fungi. Zones of inhibition were measured in millimeter and size of the disc was subtracted from the zone size to measure final activity. DMSO saturated disc served as solvent control or negative control and Streptomycin saturated discs (30 µg) for bacteria and Nystatin (30 µg) for fungi as reference or positive control.

For antifungal activities potato-dextrose agar was used with following composition.

a. Potato infusion form: 200 gms
b. Glucose: 20gms
c. Agar: 15gms
d. Distilled water: 1000 ml

For antibacterial activities against S. aureus nutrient agar with following composition was used.

a. Peptone: 5gms
b. Beef extract: 3gms
c. Sodium Chloride: 8gms
d. Agar: 15gms
e. Distilled water: 1000ml

For antibacterial activities against E. Coli Mac Conkey agar was used with following composition.

a. Peptone: 20gms
b. Lactose: 10gms
c. Bile salt: 5gms
d. Sodium chloride: 5gms
e. Neutral red: 0.075gms
f. Agar: 12gms
g. Distilled water: 1000ml

The various derivatives of iminothiazolidinone were tested for their potential to inhibit growth of different bacterial and fungal species at doses of 100 µg/ml in DMSO as a solvent, against bacterial and fungal cultures. All the compounds were found to have antimicrobial activities against different species of bacteria and fungi in our studies.

4.2 synthesis of 2-Chloro-N-(2,4-difluoro-phenyl)-acetamide (2): To a solution of (2,4-Difluoro-aniline (0.25gm, 0.0010 mole) in Dichloromethane (25 ml) chloroacetyl chloride (0.21gm, 0.0015) was added and reaction mixture was cooled at O^0C for 20 min and 2 drops of DMF added to it. reaction mixture was warmed to room temperature and kept as it is for 2 hours After completion of reaction (TLC check 4:1 Hexane: ethyl aetate). Water (30 ml) was added to it and DCM layer was separated; organic layer washed with 10% sodium bicarbonate. organic layer separated and dried over Sodium sulphate. Organic layer evaporated to get off-white solid. 83%

4.3 General procedure for N-(2,4-Difluoro-phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide (3a-m):

A mixture -Chloro-N-(2,4-difluoro-phenyl)-acetamide **(2)** (1mmol), 3-morpholino-phenol (1.15mmol) in [bmIm]OH (0.1mole) in DMF, was stirred at RT for 30 min. After completion of the reaction (TLC check), cold water was added to it and extracted with ethyl acetate (3×20 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was recrystallized using absolute ethanol to get title compound in good yields **(3a-m)**.

V. SPECTROSCOPIC DATA OF REPRESENTATIVE COMPOUNDS

N-(2,4-Difluoro-phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide (3a):

Off White solid; M.P: 117- 119 ºC.

^{1}H NMR (CDCl3, 300MHz): 3.12(t, J=4.8Hz,4H), 3.98(t, J=4.8Hz, 4H),4.05(s,2H),6.40(dd, J=2.0, 7.6Hz,1H),6.43(t, J= 2.0 Hz,1H), 6.55(dd, J=2.4,8.4Hz, 1H), 7.13 (m, 2H) 7.18(t, J=8.0Hz, 1H),7.40 (t, J = 9.8 Hz 1H),7.97(S,1H, NH).

^{19}F NMR (CDCl3, 300MHz): -115.5(1F), -120.7(1F).

IR (ATR): 1738, 1636, 1505, 1220, 962cm^{-1}.

MS (m/z): 349.34 [M^+ +1] ;($C_{18}H_{18}F_2N_2O_3$)

N-(2,6-Difluoro-phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide(3b)

Off White solid; M.P: 132- 134 ºC.

^{1}H NMR ($CDCl_3$, 300MHz)*:* δ 3.14(t, J=4.8Hz,4H), 3.97(t, J=4.8Hz, 4H),4.02 (s,2H), 6.34(dd, J=2.0, 7.6Hz, 1H) 6.42 (dd, J=2.0, 7.6Hz, 1H), 6.45(t, J=2.0Hz, 1H), 6.56(dd, J=2.4,8.4Hz, 1H) 6.91-6.97 (m, 2H), 7.05-7.15 (m, 1H).7.82(S,1H, NH)

^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -122.6 (d, 2F).

MS (m/z): 349.34 [M^+ +1]; $C_{18}H_{18}F_2N_2O_3$

IR (ATR): 1743, 1636, 1465, 999, 783 cm^{-1}.

N-(3,4-Difluoro-phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide (3c)

Off White solid; M.P: 143- 145 ºC.

^{1}H NMR ($CDCl_3$, 300MHz): 3.16(t, J=4.8Hz,4H), 3.98(t, J=4.8Hz, 4H),4.05 (s,2H), 6.34(dd,J=2.0, 7.6Hz, 1H) 6.42 (dd, J=2.0, 7.6Hz, 1H), 6.45(t, J=2.0Hz, 1H), 6.56(dd, J=2.4,8.4Hz, 1H), 6.58-6.61(t, J = 9.2 Hz, 1H), 6.68-6.75 (t(d), J = 10.17 & 2.24 Hz, 1H),7.01-7.10 (q, J = 9.2 Hz,1H) ,7.80 (s,1H, NH)

^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -113.9 (d, 1F), -120.3 (t, 1F).

MS (m/z): 349.34 [M^+ +1]; $C_{18}H_{18}F_2N_2O_3$

IR (ATR): 1738, 1636, 1505, 1200,787 cm-1.

N-(3,5-Difluoro-phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide (3d)

Off White solid; M.P.: 133-135 ºC.

^{1}H NMR ($CDCl_3$, 300MHz): δ 3.14(t, J=4.8Hz,4H), 3.97(t, J=4.8Hz, 4H),4.01 (s,2H), 6.35(dd, J=2.0,.6Hz,1H) 6.41 (dd, J=2.0,7.6Hz, 1H), 6.47(t, J=2.0Hz, 1H), 6.58(dd, J=2.4,8.4Hz,1H), 6.83-6.98(m,3H),7.83(s,1H, NH)

^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -108.4 (s,2F).

MS (m/z): 349.34 [M^+ +1]. $C_{18}H_{18}F_2N_2O_3$

IR (ATR): 2987(C-H), 1710(C=O), 1631, 1497, 1366, 125, 1093, 905 cm^{-1}.

2-(3-Morpholin-4-yl-phenoxy)-N-(2,4,5-trifluoro-phenyl)-acetamide (3e)

Off White solid; M.P.: 141-143 ºC.

^{1}H NMR ($CDCl_3$, 300MHz): δ 3.16(t, J=4.8Hz,4H), 4.01(t, J=4.8Hz, 4H),4.10(s,2H), 6.36(dd, J=2.0, 7.6Hz, 1H), 6.40(t, J=2.0Hz, 1H), 6.53(dd, J=2.4, 8.4Hz, 1H), 6.81-6.90 (m, 1H), 6.99-7.08 (m, 1H), 7.13(t, J=8.0Hz, 1H),7.88(S,1H, NH).

^{19}F NMR ($CDCl_3$, 282MHz)*:* -126 (d, 1F), -138 (d, 1F), -141(dd, 1F).

MS (m/z): 367.33 [M^+ +1]. $C_{18}H_{17}F_3N_2O_3$

IR (ATR): 2988(C-H), 1709(C=O), 1630(C=N), 1495(C=C), 1367(C-NCH2), 1337(C-N), 1093(C-CF_3), 843(O-substituted Ph ring), 812(C-S-C) cm^{-1}.

N-(2,4-Difluoro-benzyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide (3f)

Off White solid; M.P.: 111-113 ºC.

^{1}H NMR ($CDCl_3$, 300MHz): δ 3.17(t, J=4.8Hz,4H), 4.02(t, J=4.8Hz, 4H),4.15(s,2H), 4.59 (d, *J* =4.0 Hz, 2H) 6.38(dd, J=2.0,7.6Hz, 1H),6.42(t, J=2.0Hz,1H),6.55(dd, J=2.4, 8.4Hz, 1H), 6.85(m, 2H), 7.13(t, J=8.0Hz, 1H),7.36 (q, *J* = 8.1 Hz 1H), 7.88(S,1H, NH).

^{19}F NMR ($CDCl_3$, 282MHz)*:* --111.6 (d, 1F), -114.4(d, 1F)

MS (m/z): 363.37 [M^+ +1]. $C_{19}H_{20}F_2N_2O_3$

IR (ATR): 1715, 1607, 1510 1368, 1333, 1106 ,863 cm^{-1}.

N-(3-Chloro-4-fluoro-phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide (3g)

Off White solid; M.P.: 155-157 ºC.

^{1}H NMR ($CDCl_3$, 300MHz): δ 3.17(t, J=4.8Hz,4H), 4.02(t, J=4.8Hz, 4H),4.15(s,2H), 6.38(dd, J=2.0,7.6Hz, 1H),6.42(t, J=2.0Hz,1H),6.55(dd, J=2.4, 8.4Hz, 1H), 6.99 (m, 2H), 7.24 (dd, J = 4.0 & 2.2 Hz, 1H),7.46 (t, J = 8.7 Hz,1H), 7.81(S,1H, NH).

^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -121.6 (s,1F)

MS (m/z): 365.80 [M^+ +1]. $C_{18}H_{18}ClFN_2O_3$

IR (ATR): 1715, 1637, 1508, 1373, 1314, 1204, 878, cm^{-1}.

2-(3-Morpholin-4-yl-phenoxy)-N-(2-trifluoromethyl-phenyl)-acetamide (3h)

Off White solid; M.P.: 147-149 ºC.

^{1}H NMR (CDCl3, 300MHz): 3.19(t, J=4.8Hz,4H), 4.06(t, J=4.8Hz, 4H),4.20(s,2H), 6.40 (dd, J=2.0,7.6Hz, 1H),6.45(t, J=2.0Hz,1H),6.60(dd, J=2.4, 8.4Hz, 1H), 7.02(d, J = 7.9 Hz 1H), 7.15(t, J=8.0Hz, 1H), (7.20 (t, J = 7.8 Hz, 1H),7.46 (t, J = 7.8 Hz,1H),7.61(d, J = 7.7 Hz 1H), 7.90(S,1H, NH).

^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -62.1 (s,3F)

MS (m/z): 381.36 [M^+ +1]. $C_{19}H_{19}F_3N_2O_3$

IR (ATR): 2361, 1680, 1599, 1135, 784 cm^{-1}

2-(3-Morpholin-4-yl-phenoxy)-N-(3-trifluoromethyl-phenyl)-acetamide (3i)
Off White solid; M.P: 137- 139 °C.
^{1}H NMR (CDCl3, 300MHz) : δ 3.17(t, J=4.8Hz,4H), 4.08(t, J=4.8Hz, 4H),4.19(s,2H), 6.41 (dd, J=2.0,7.6Hz, 1H),6.46(t, J=2.0Hz,1H),6.62(dd, J=2.4, 8.4Hz, 1H), 7.09(d, J = 8.6 Hz 1H), 7.15(t, J=8.0Hz, 1H), 7.29 (t, J = 2.7 Hz, 1H),7.47 (bs, J = 6.2 Hz,2H), 7.92(S,1H, NH).
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -61.5 (s,3F)
MS (m/z): 381.36 [M^+ +1].; $C_{19}H_{19}F_3N_2O_3$
IR (ATR): 1730, 1641, 1446, 1327, 1122,899,794 cm^{-1}
2-(3-Morpholin-4-yl-phenoxy)-N-(4-trifluoromethyl-phenyl)-acetamide (3j)
Off White solid; M.P.: 171-173 °C.
^{1}H NMR (CDCl3, 300MHz): δ 3.19(t, J=4.8Hz,4H), 4.10(t, J=4.8Hz, 4H),4.20(s,2H), 6.43 (dd, J=2.0,7.6Hz, 1H),6.48(t, J=2.0Hz,1H),6.64(dd, J=2.4, 8.4Hz, 1H), 7.19(t, J=8.0Hz, 1H), 7.40(d, J = 7.8 Hz 2H), 7.66 (d, J = 7.8 Hz 2H),7.92(S,1H, NH).
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -62.1 (s,3F)
MS (m/z): 381.36 [M^+ +1]. $C_{19}H_{19}F_3N_2O_3$
IR (ATR1738, 1643, 1603, 1316, 1111, 841,738 cm^{-1}
N-(4-Trifluoromethoxy -phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide (3k)
Off White solid; M.P.: 162-164 °C.
^{1}H NMR (CDCl3, 300MHz): δ 3.16(t, J=4.8Hz,4H), 4.07(t, J=4.8Hz, 4H),4.16(s,2H), 6.39 (dd, J=2.0,7.6Hz, 1H),6.44(t, J=2.0Hz,1H),6.60(dd, J=2.4, 8.4Hz, 1H), 6.90(d, J = 8.85 Hz 2H), 7.18 (m, 3H),7.92(S,1H, NH) MS (m/z): 398.39 [M+ +1].; $C_{19}H_{19}F_3N_2O_4$
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -58.1 (s,3F).
IR (ATR): 1739, 1638, 1501, 1254, 1177, 1160, 996,788 cm^{-1}
N-[3,5-Dichloro-4-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-2-(3-morpholin-4-yl-phenoxy)-acetamide (3l)
White solid; M.P: 127- 129 °C.
^{1}H NMR (CDCl3, 300MHz): δ 3.14(t, J=4.8Hz,4H), 4.03(t, J=4.8Hz, 4H),4.12(s,2H), 6.28 (tt) J=1J{HF}=55.8 Hz,1H), 6.39(dd, J=2.0,7.6Hz, 1H),6.44(t, J=2.0Hz,1H),6.60(dd, J=2.4, 8.4Hz, 1H), , 7.12-7.14 (d, J= 8.7 Hz 1H), 7.28 (bs,2H),7.70(S,1H, NH).
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -87.8 (t, 2F,-138.2(t, 2F)
MS (m/z): 497.27 [M+ +1].; $C_{20}H_{18}Cl_2F_4N_2O_4$
IR (ATR): 1741, 1638,1457,1280,1112,859 cm^{-1}.
N-(4-Fluoro-phenyl)-2-(3-morpholin-4-yl-phenoxy)-acetamide (3m)
White solid; M.P.: 146-148 °C.
^{1}H NMR (CDCl3, 300MHz): δ 3.15(t, J=4.8Hz,4H), 4.05(t, J =4.8Hz, 4H),4.15(s,2H), 6.39 (dd, J=2.0,7.6Hz, 1H),6.43(t, J=2.0Hz,1H),6.58(dd, J=2.4, 8.4Hz, 1H), 7.11 (dd, 8.7 Hz, 2H), 7.15(t, J=8.0Hz, 1H), 7.43 (d, J= 8.7 Hz 2H),7.92(S,1H, NH).
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -121.6(s,1F)
MS (m/z): 331.35 [M^+ +1].; $C_{18}H_{19}FN_2O_3$
IR (ATR): 1709, 1628, 1501, 1254, 1177, 1160,859 cm^{-1}

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VII. CONFLICT OF INTEREST:

The authors declared that they had no conflicts of interest.

VIII. REFERENCES

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