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SYNTHESIS AND CHIRAL SEPARATION OF SOME PYRAZOLE FUSED PIPERIDINES

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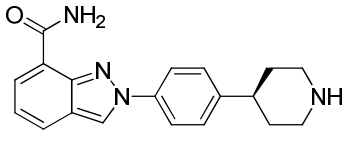
ABSTRACT

Novel synthetic strategy for the preparation of pyrazole fused piperidine is developed. This concise synthesis of novel pyrazole fused piperidine derivatives can be a useful approach to generate potent chemotherapeutic agents in developing new drug candidates. Synthesised pyrazole fused piperidine derivative is separated by chairal preparative HPLC and characterised by chairal HPLC and SOR datas.

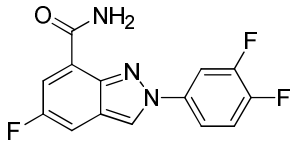
Keywords *– pyrazole fused piperidine, racemic, enatiomer, SOR, ^{1}HNMR, ^{19}FNMR, MS*

1. INTRODUCTION

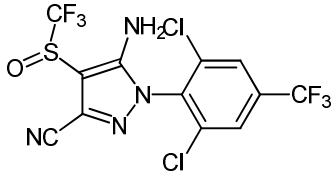
Pyrazole fused piperidine and its derivatives have gained considerable importance in medicinal chemistry in view of their promising pharmacological properties.[1-2] Several indazoles are found to exhibit significant levels of activity as HIV protease inhibitors.[3-4] Serotonin 5-$HT_{1\alpha}$, 5-HT_2[5] and 5-HT_3 receptor antagonists,[6-7] acetylholinesterase inhibitors,[8] whereas 1-[3-(dimethylamino)-propyl]-5methyl-3-phenyl-1*H*-indazole (FS-32),[2] MK-4827 and compound **1 (Figure 12)** have been shown to be a potent antidepressant drug candidates and PARP 1 inhibitors.[9]



MK- 4827 (1)



(2)



Fipronil (3)

Figure 12: Potent drug candidates containing fused pyrazole moiety

Pyrazole fused piperidine or tetrahydroazaindzoles which have been reported to inhibit proto-porphyrinogen oxidase (PPO), and enzyme which catalyzes the oxidation of protophorphirinogen to protoporphyrin and is the site of action of membrane disrupting herbicides.[10]

Pyrazolopiperidines are a promising class of heterocyclic compounds and have been shown to be inhibitors of cyclin- dependent protein kinase-2 (cdk-2), cyclin-dependent protein kinase-5 (cdk-5), and phosphatidylinositol 3-kinase (PI3- K).[11-12] Thus these compounds have potential in the treatment of several diseases, including bipolar disorder, diabetes, dementia, Alzheimer's disease, schizophrenia, depression, and cancer.[12]

Several methods for the synthesis of indazoles and their derivatives have been reported in the literature.[13-15] Most of them involve the construction of the pyrazole moiety starting from preconstructed benzene derivatives. On the other hand, methods based on pyrazole precursors, more easily accessible, are briefly described in the literature. [16] The introduction of fluorine atoms into organic molecules has proven to be a valuable tool for changing the physical and chemical properties of the compound without major steric implications.[17-18] In that respect, there is a growing demand for synthetic methods for the preparation of selectively fluorinated heterocyclic compounds used in pharmaceutical and agrochemical industries.[19] Consequently, fluorinated pyrazoles are of specific interest because the introduction of a fluorine atom can drastically affect the biological properties of this class of heterocyclic compounds.[20-21] In continuation of our work on the development of synthetic methodology,[22-24.] We now reported an efficient synthesis of *N*-(5-allyl-7,7-difluoro-2-(2,4-difluorophenyl) tetrahydroindazole analogs involving, mannich reaction, Dieckamn cyclization, followed by cyclocondensation of (2-fluoro-4-halogeno-phenyl)-hydrazine with the cyanoketone intermediate (scheme 1).

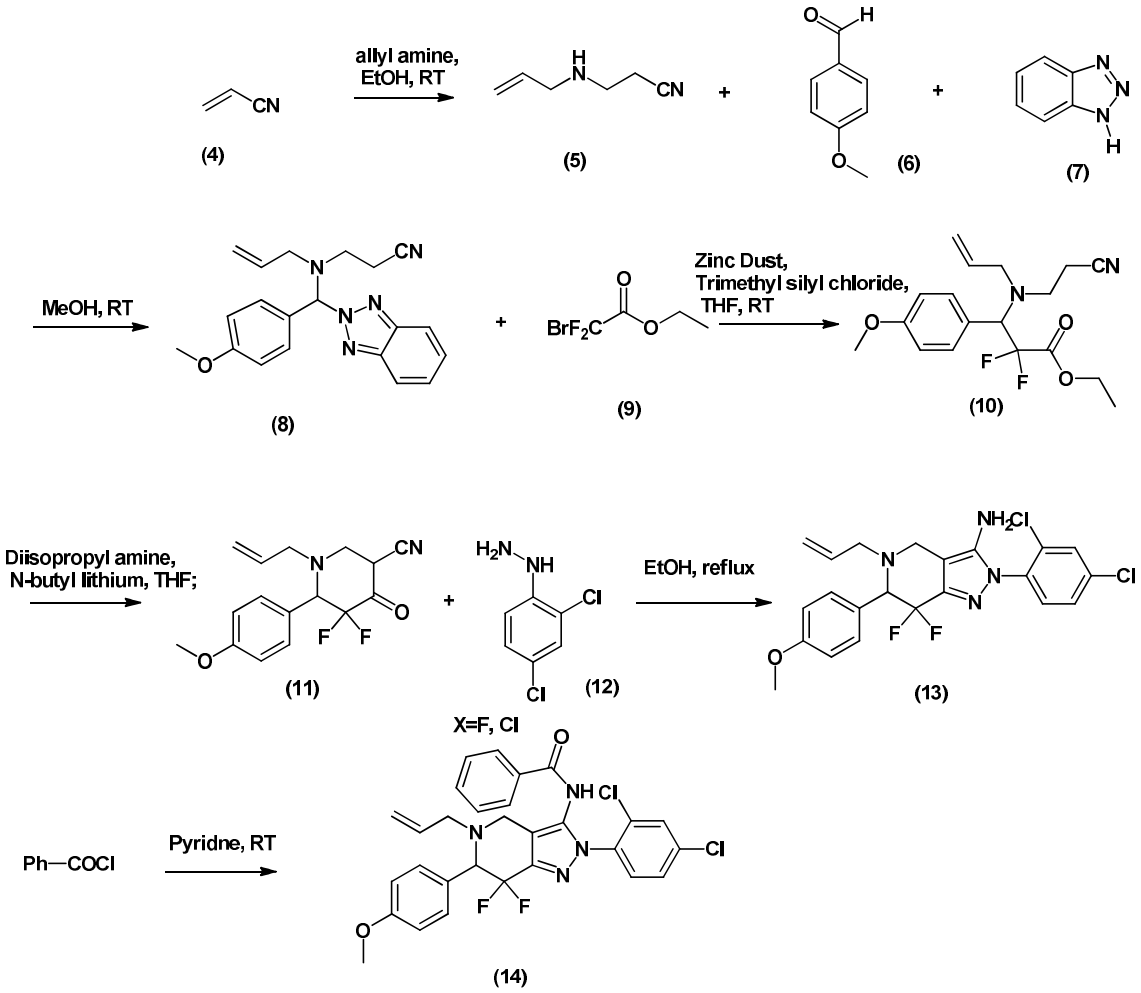
2. MATERIALS AND METHODS

All analytical thin layer chromatography was performed with E. Merck silica gel $60F_{254}$aluminum sheets and was visualized with UV light. The following mobile phases were employed for TLC: chloroform, methanol and hexane, ethyl acetate in different ratio's. The instrumental techniques employed for the characterization of the newly synthesized compounds includes ^{1}H NMR and mass spectroscopy. The details of instrumentation are briefly given below. ^{1}H NMR (400 MHz) spectra were recorded on $CDCl_3$, DMSO-d_6 solution in a 5 mm tube on a BRUKER amx 400 and 300 Fourier transform spectrophotometer (at SIF, Indian Institute of Science, Bangalore, India) with tetramethylsilane (TMS) as internal standard. The spectrophotometer was internally locked to the deuterium frequency of the solvent. Chemical shifts were recorded in ppm relative to TMS. Mass and purity were recorded on a LC–MSD-Trap-XCT.

3. RESULTS AND DISCUSSION

Our synthetic approach **(Scheme 1)**[23] begins with the addition of allylamine with acrylonitrile **(3)** gave the compound **(4)**. This was converted to benzotriazole derivative (**5)** by reaction with 4-methoxy benzaldehyde **(6)** and benzotriazole**(7)**. Compound **(8)** was prepared staring from 2-bromo-2,2-difluoroacetate**(9)** via benzotriazole derivative **(10)** using Reformatsky reaction in THF under nitrogen atmosphere. A Dieckmann condensation of **(11)** with strong base in-situ generated LDA at -78 ^{o}C yields cyano ketone **(11)**. The reactivity of the carbonyl ester was increased towards the nucleophille due to the presence of the geminal-difluoro group. The Dieckmann cyclization was optimized in the presence of various bases (NaH, K-*t*-BuO-, *n*-BuLi) and solvents. The best results was obtained when **(10)** was reacted with LDA at -78^{o}C for three hours furnishing the product cyano ketone. Synthetic entries into the desired 3,4-bicylic system are typically multistep sequences based on the condensation of 2,4 difluoro phenyl hydrazine**(112)** and cyclocyano ketone **(11)** yields **(13)**. Several synthesis of isomeric 4,5-fused bicylclicpyrazoles or tetrahydroindazoles have been reported. However, to best our knowledge there is no report for the synthesis of *N*-(5-allyl-7,7-difluoro-1-(2,4-difluorophenyl)

tetrahydroindazolanalogs. Here, we report an efficient, versatile and convenient synthetic route, which provide rapid access to pyrazole fused piperidines. The cyclocondensation of hydrazines with cyclic *β*-cyanoketone under neutral conditions generally leads to *N*-(5-allyl-7,7-difluoro-2-(2,4-difluorophenyl)tetrahydroindazolanalogs. The more reactive ketone and terminal NH_2 group of the arylhydrazine react first leading to the formation of **(13)**. In order to attain the regioselectivity of these reactions we attempted many conditions like the reaction of binulecophile phenyl hydrazine with cyano ketone in the presence of NaH, it was unsuccessful as we observed decomposition product. We also explored a strategy by using Boc protected phenyl hydrazine but we were unsuccessful. The primary amine of tetrahydraindazoles **(13)** was derivatised to give the corresponding tetrahydroindazole carboxymides by the treatment with benzoyl chloride.

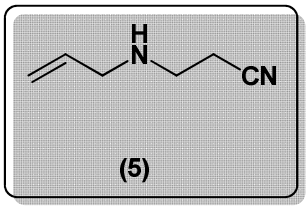


Scheme 1: Synthetic pathway for the preparation of novel pyrazole fused piperidines.

4. EXPERIMENTAL METHODS

Procedure for the synthesis of 3-3(allylamino)propanenitrile (5): To a solution of acrylonitrile **(4)** (23.2 g, 438 mmol) in ethanol (250 mL) at 0 ^{o}C under nitrogen, allyl amine (25 g, 438 mmol) in ethanol was added slowly and then it was stirred at room temperature for overnight. The reaction was monitored by LCMS, after completion of the reaction the reaction, mass was concentrated completely to yield the product **(5)** pale yellow colored oil, 45 g (93.7%).

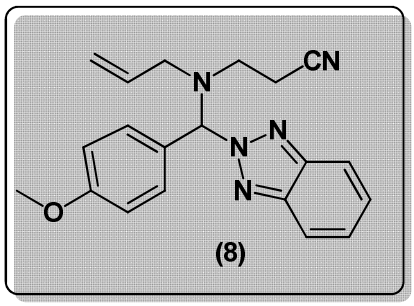
Characterization data of **3-3(allylamino) propane nitrile (5):**



(5)

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 5.75-5.85 (m, 1H), 5.15 (dd, *J*=1.36 Hz and 15.72 Hz, 1H), 5.03 (dd, *J*=0.52 Hz and 10.12 Hz, 1H), 3.14 (d, *J*=5.72 Hz, 2H), 2.70 (t , *J*=6.8 Hz, 2H), 2.55 (t, *J*=6.48 Hz, 2H), 2.50 (m, NH).

Procedure for the synthesis of3-(*N*-((2*H*-Benzo[d][1,2,3]triazol-2-yl)(4-methoxyphenyl)methyl)-N- allylamino)propanenitrile (8):

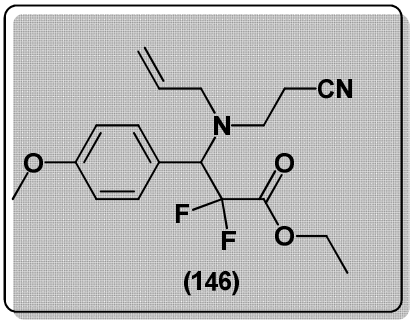


(8)

To the solution of 3-3(allylamino)propanenitrile **2** (45 g, 408.5 mmol)in methanol (450 mL) under nitrogen, was added benzotriazole (48.6 g, 408.5 mmol) followed by 4-methoxy benzaldehyde(61.15 g, 449.5 mmol). Then reaction mass was stirred at room temperature for overnight. The reaction was monitored by TLC once the reaction was completed, reaction mass was concentrated and this was taken as such for next step without doing any further purification. Due to stability problem this was as taken as such for next step. Crude yield 135g (95.0%) light brown colored oil.

Procedure for the synthesis ofEthyl 3-(allyl)2-cyanoethyl)amino)-2,2-difluro-3-(4-methoxyphenyl) propanate (10): To a suspension of zinc dust(18.4 g, 288 mmol) in dry THF (350 mL) under nitrogen was added Trimethylsilyl chloride(16.3 g, 151 mmol). After 10 minutes ethyl bromodifluoro acetate (32g, 158 mmol) was slowly added, stirred for 10 minutes. Then added a solution of 3-(*N*-((2*H*-Benzo[d][1,2,3]triazol-2-yl)(4-methoxyphenyl)methyl)-N-allylamino)propanenitrile(**8**) (50 g, 144 mmol) in THF (150 mL) was added slowly. The reaction mass stirred at room temperature for 12 hours. Then reaction mixture was poured on 5% aqueous $NaHCO_3$ and filtered on celite bed. The layers were separated and aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with water, brine and dried over Na_2SO_4 and concentrated. The crude obtained was purified by flash column chromatography by using hexane: ethyl acetate as eluent to yield the product.(**10**) 31 g (61%); Pale yellow colored oil.

Characterization data of **Ethyl 3-(allyl)2-cyanoethyl)amino)-2,2-difluro-3-(4-methoxyphenyl)propanate(10):**



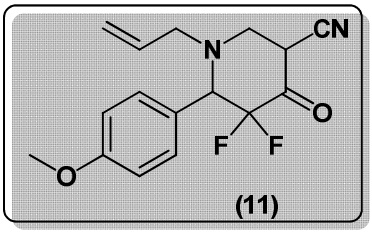
(146)

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 7.41 (d, *J*=8.64 Hz, 2H), 6.97 (d, *J*=8.76 Hz, 2H), 5.60-5.70 (m, 1H), 5.12-5.21 (m, 2H), 4.50 (dd, *J*=8.16 Hz and 26.44 Hz, 1H), 4.32 (q, *J*=5.7 Hz, 2H), 3.76 (s, 3H), 3.46-3.50 (m, 1H), 2.77-2.82 (m, 1H), 2.69-2.75 (m,1H), 2.53-2.68 (m, 2H),

2.40-2.49 (s, 1H), 1.27 (t, *J*=7.12 Hz, 3H); Coupled ^{19}F NMR (376.5 MHz, DMSO-d_6):δ= -101.1 (dd, $J_{H\text{-}F}$=7.21 Hz, $J_{F\text{-}F}$=254 HZ, 1F), -114,2 (dd, $J_{H\text{-}F}$=26 Hz, $J_{F\text{-}F}$=254 Hz, 1F); Decoupled ^{19}F NMR (376.5 MHz, DMSO-d_6):δ= -101.15 (d, $J_{F\text{-}F}$=254 HZ, 1F), -114,27 (d, $J_{F\text{-}F}$=254.3 Hz, 1F); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 13.6, 16.3, 46.0, 53.7, 54.8, 55.04, 62.9, 113.8, 114.5, 117.0, 118.1, 119.3, 122.2, 131.5, 131.8, 135.7, 159.4, 163.2; MS (ESI + ion): m/z=353.2; Anal. Cacld for $C_{18}H_{22}F_2N_2O_3$ C, 61.35; H, .6.29; N, 7.95.Found: C, 61.36; H, 6.15; N, 7.90.

Procedure for the synthesis of1-allyl-5,5-difluro-6-(4-methoxyphenyl)-4-oxopiperidine-3-carbonitrile (11): To a solution of diisopropyl amine(20.7 g, 408 mmol) in THF (1 Litre) under nitrogen at -78 ^{o}C was added *n*-butyl lithium(12.15 g, 187 mmol) and then it was stirred at -78 ^{o}C for 1 hour. Then a solution of ethyl 3-(allyl)2-cyanoethyl)amino)-2,2-difluro-3-(4-methoxyphenyl) propionate **(11)** (30 g, 85 mmol) in THF was added slowly at -78 ^{o}C for duration of one hour. Then reaction mixture was slowly brought to room temperature and stirred for 12 hours. After completion of the reaction, reaction mass was quenched with saturated NH_4Cl solution (250 mL) at 0 ^{o}C and then extracted with ethyl acetate. Then combined organic layer was washed with water, brine solution and dried over Na_2SO_4 and concentrated. The crude obtained was purified by column chromatography by using hexane: ethyl acetate (50%) as eluent to get **(11)**. Yield 16.5 g (63.46%).

Characterization data of **1-allyl-5,5-difluro-6-(4-methoxyphenyl)-4-oxopiperidine-3-carbonitrile (11):**



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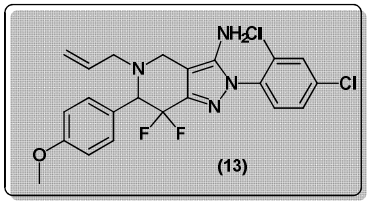
^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.37 (d, *J*=8.36 Hz, 2H), 6.95 (d, *J*=8.56 Hz, 2H), 5.80 (m, 1H), 5.29 (m, 2H), 4.53 (m, 1H), 3.84 (s, 3H), 3.57-3.60 (m, 1H), 3.22 (m, 1H), 2.98-3.01 (m, 1H), 2.57-2.637 (m, 2H); Coupled ^{19}F NMR (376.5 MHz, DMSO-d_6):δ= -89.66 (d, $J_{F\text{-}F}$= 257.2 Hz, 1F), -102.59 (d, $J_{F\text{-}F}$= 257.56 Hz, 1F); Decoupled ^{19}F NMR (376.5 MHz, DMSO-d_6):δ= -89.65 (d, $J_{F\text{-}F}$= 260.2 Hz, 1F), -102.60 (d, $J_{F\text{-}F}$= 260.01 Hz, 1F); ^{13}C NMR (DMSO-d_6, 100 MHz): δ= 17.1, 46.5, 53.4, 55.2, 64.6, 114.0, 118.6, 119.7, 121.9, 122.6, 131.4, 131.5, 131.7, 134.4, 135.5, 159.9; MS (ESI + ion): m/z=307.2; Anal. Cacld for $C_{16}H_{16}F_2N_2O_3$ C, 62.74; H, 5.26; F.12.40; N, 9.15; O, 10.45. Found: C, 62.81; H, 5.21; N, 9.19.

Procedure for the synthesis of5-allyl-7,7-difluoro-2-(2,4-difluorophenyl)-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridine-3-amine (13): The solution of 1-allyl-5,5-difluro-6-(4-methoxyphenyl)-4-oxopiperidine-3-carbonitrile **(11)** (15 g, 49 mmol), (2,4-diflurophenyl)-hydrazine **(12)** (9.7 g, 53.5 mmol) in ethanol (450 mL) was refluxed to overnight under nitrogen, and monitored by TLC. After completion of the reaction, this was concentrated completely and the crude product was purified by column chromatography using hexane:ethyl acetate (1:1) as eluent to yield 6.5g (30%) of compound **13**.

Characterization data of **5-allyl-7, 7-difluoro-2-(2,4-difluorophenyl)-4, 5, 6, 7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4, 3-c]pyridine-3-amine 13:**



^{1}H NMR (400 MHz, DMSO-d_6): white solid, mp89-90 ^{o}C; IR (neat) ν_{max}, 3440.5, 3303.0, 3169.4, 1639.6, 1606.4, 1506.4, 1493.5, 1298.2, 1245.1, 1178.9, 997.0 cm ^{1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 7.51-7.62 (m, 2H), 7.23-7.28 (m, 1H), 7.16 (d, *J*=8.52 Hz, 2H), 6.95 (d, *J*=8.68 Hz, 2H), 5.77-5.87 (m, 1H), 5.55 (s, 2H), 5.15-5.20 (m, 2H), 4.22-4.27 (m, 1H), 3.76 (s, 3H), 3.40-3.44 (m, 1H), 3.29-3.33 (m, 1H), 3.06-3.11 (m, 1H), 2.97-3.01 (m, 1H*);* Coupled^{19}F NMR (DMSO-d_6, 376.5 MHz): δ= -90.3 (d, $J_{F\text{-}F}$=256 Hz, 1F), -102.1 (d, $J_{F\text{-}F}$=256 Hz, 1F), -108.36 to -108.44 (m,1F), -115.97 to -116.05 (m, 1F); Decoupled^{19}F NMR (DMSO-d_6, 376.5 MHz): δ= -90.35 (d, $J_{F\text{-}F}$=259.5 Hz, 1F), -102.1 (d, $J_{F\text{-}F}$=258.5 Hz, 1F), -108.40 (d, $J_{F\text{-}F}$=8.13 Hz, 1F), -116.01 (d, $J_{F\text{-}F}$=7.90 Hz, 1F); ^{13}C NMR (DMSO-d_6,100 MHz): δ= 44.5, 55.4, 56.9, 69.2, 98.0, 112.5, 112.7, 114.0, 118.1, 124.1, 131.3, 131.5, 135.8, 143.9, 159.5; MS (ESI + ion): m/z =433.0; Anal. Cacld for $C_{22}H_{20}F_4N_4O$; C, 61.11; H, 4.66; N, 12.96 Found: C, 61.20; H, 4.50; N, 12.93.

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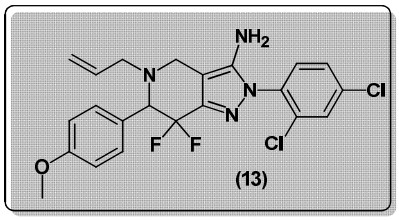
Procedure for the synthesis of5-allyl-2-(2,4-dichlorophenyl)-7,7-difluoro-6-(4-methoxyphenyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-amine (13)

The solution of 1-allyl-5,5-difluro-6-(4-methoxyphenyl)-4-oxopiperidine-3-carbonitrile **(11)** (5 g, 16.3mmol), (2,4-dichlorophenyl)-hydrazine**(12)** (3.4 g, 19.6mmol) in ethanol (150 mL) was refluxed to overnight under nitrogen, and monitored by TLC. After completion of the reaction, this one was concentrated completely and the crude product was purified by column chromatography using hexane:ethyl acetate (1:1) as eluent to yield 4.2g (56%) of compound **(13)**.

Characterization data of **5-allyl-2-(2, 4-dichlorophenyl)-7, 7-dichloro-6-(4-methoxyphenyl)-4, 5, 6, 7-tetrahydro-2H-pyrazolo[4, 3-c]pyridin-3-amine (13)**

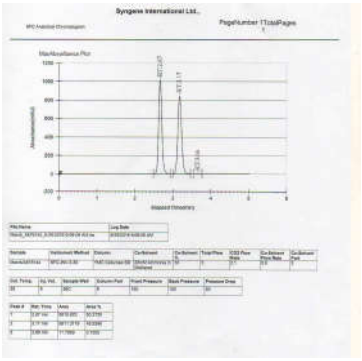


(13)

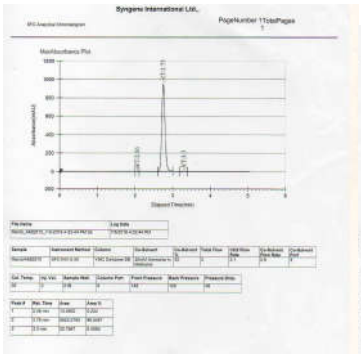
white solid, mp98-100 ^{o}C; IR (neat) ν_{max} 3220 (br), 3440.5, 3303.0, 3169.4, 1639.6, 1616.4, 1506.4, 1493.5, 1298.2, 1245.1, 1178.9, 1140.5, 1037.4 cm ^{1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ= 7.88 (s, 1H), 7.54-7.60 (m, 2H), 7.15 (d, *J*=8.6 Hz, 2H), 6.93 (d, *J*=8.68 Hz, 2H), 5.77-5.85 (m, 1H), 5.49 (s, 2H), 5.14-5.20 (m, 2H), 4.21-4.27 (m, 1H), 3.75 (s, 3H), 3.40-3.43 (m, 1H), 3.25-3.30 (m, 1H), 3.06-3.11 (m, 1H), 2.95-3.00 (m, 1H); Coupled ^{19}F NMR (DMSO-d_6, 376.5 MHz): δ= -89.66 (d, $J_{F\text{-}F}$=258.7 Hz, 1F), -102.59 (d, $J_{F\text{-}F}$=257.6 Hz, 1F); Decoupled ^{19}F NMR (DMSO-d_6, 376.5 MHz): δ= -89.66 (d, $J_{F\text{-}F}$=258.43 Hz, 1F), -102.59 (d, $J_{F\text{-}F}$=257.38 Hz, 1F); ^{13}C NMR (DMSO-d_6, 100 MHz): δ= 44.0, 55.0, 56.5, 68.3, 97.1, 113.5, 115.4, 117.7, 123.5, 128.3, 129.9, 131.1, 133.0, 134.6, 135.4,143.2, 159.0;MS (ESI + ion): m/z =467.0; Anal. Cacld for $C_{28}H_{30}F_4N_4O_2$; C, 56.39; H, 4.33; N, 12.04; Found: C, 56.83; H, 4.29; N, 12.09.

General procedure for the synthesis of 14(a-b): To a solution of 5-allyl-7,7-difluoro-2-(2,4-difluorophenyl)-4,5,6,7-tetrahydro-6-(4-methoxyphenyl)-2H-pyrazolo[4,3-c]pyridine-3-amine **(13)** in pyridine at 0 ^{o}C under nitrogen atmosphere, acid chloride was added and then it was stirred at room temperature for overnight. After completion of the reaction, 10% $NaHCO_3$ solution was added and extracted with ethyl acetate. Then combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4 and concentrated. The crude obtained was purified by column chromatography by using Hexane: ethyl acetate (50%) to yield the pure product.

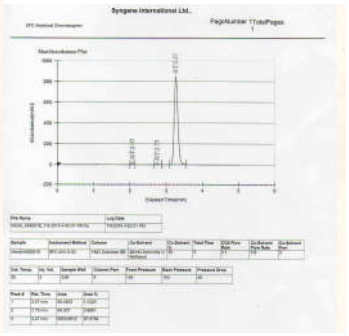
Piperidine derivative **14** synthesized by **Scheme 1** is recemic in nature and it is consist of two enantiomers present in each of derivatives were resolute by mechanical separation technique chairal HPLC. Separated enetiomers were characterised by chairal HPLC and SOR.



Chairal HPLC of comound **14a**



Chairal HPLC of comound **14a$_1$**



Chairal HPLC of comound **14a$_2$**

SOR [α]$^{25}_{D}$ (+)112.93 (C=1, $CHCl_3$) SOR [α]$^{25}_{D}$ (-)110.53 (C=1, $CHCl_3$)

5. CONCLUSION

Novel piperidine fused pyrazoles were synthesised by adopting a concise multi-step strategy, which provides feasible reaction conditions and good yield. The amide derivative of Novel piperidine fused pyrazole is separated by chairal preparative HPLC method and characterised by chairal HPLC and SOR datas.

6. CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Caron, S.; Vazquez, E. A Versatile and Efficient Synthesis of Substituted 1H-Indazoles. *Synthesis.* 1999, 4, 588.

2. Yeu, J.P.; Yeh, J. T.; Chen, T. Y. An Expedient Synthesis of 1-[3-(Dimethylamino)propyl]-5-methyl-3-phenyl-1*H*-indazole (FS-32) - An Antidepressant. *Synthesis.* 2001, *48.* 1775.

3. Sun, J. H.; Teleha, C. A.; Yan, J. S.; Rodgers, J. D.; Nugiel, D. A. Efficient Synthesis of 5-(Bromomethyl)- and 5-(Aminomethyl)-1-THP-Indazole. *J.Org. Chem*. 1997, *62*, 5627.

4. Rodgers, J. D.; Johnson, B. L.; Wang, H.; Greenberg, R. A.; Erickson-Viitanen, S.; Klabe, R. M.; Cordova, B. C.; Rayner, M. M.; Lam, G. N,; Chang, C. H. Synthesis of 1H-indazole: a combination of experimental and theoretical studies. *Bioorg. Med.Chem. Lett.* 1996, *6*, 2919.

5. Norman, M. H.; Navas, F.; Thomson, J. B.; Rigdon, G. C. Synthesis and Evaluation of Heterocyclic Carboxamides as Potential Antipsychotic Agents. *J. Med. Chem*. 1996, *39*, 4692.

6. Koide, T.; Matsuhita, H. Influence of a chronic new potential antidepressant, 1-[3-(dimethylamino)propyl]-5-methyl-3-phenyl-1H-indazole(FS32) and its N-Desmethylated compound(FS97): Treatment on monoaminergic receptor sensitivity in the rat brain. *Neuropharmacology.*1981, *20*, 285-292.

7. Jagtap, P.; Szabo, C. Poly(ADP-ribose) polymerase and the therapeutic effects of its inhibitors. *Nat. Rev. Drug Discovery.* 2005, *4*, 421–440.

8. Schreiber, V.; Dantzer, F.; Ame, J.C.; Murcia, G. Poly(ADP-ribose): novel functions for an old molecule. *Nat. Rev. Mol. Cell. Biol*. 2006, *7,* 517–528.

9. Scarpelli, R.; Boueres, J. K.; Cerretani, M.; Cerretani, F.; Ontoria, M.O.; Rowley, M.; Fademrecht,C. S.; Toniatti, C.; Jones, P. Synthesis and biological evaluation of substituted 2-phenyl-2*H*-indazole-7-carboxamides as potent poly(ADP-ribose) polymerase (PARP) inhibitors. *Bioorganic & Medicinal Chemistry Letters.* 2010*, 20* , 488-492.

10. Wolf, A.D. Herbicidal 2-substituted phenyl-4, 5, 6, 7-tetrahydro-2H-indazoles. *US patent.* 4059434, 1977.

11. Dress, B.E.; Chakravarty, L.; Prestwich, G.D.; Dorman, G.; Kavecz, M.; Lukacs, A.; Urge, L.;Darvas, F.; Rzepecki, P.W.; Ferguson, C.G. Compounds having inhibitive activity of

12. phosphatidylinositol 3-kinase and methods of use thereof. W.O. Patent 016,245, 2005; *Chem*.

13. *Abstr*. **2005**, *142*, 261534.

14. Kung, D. W. S.; Fuller, G. Pyrazolo[3,4-b]pyridin-6-ones as GSK-3 inhibitors. U.S. Patent 266,815, 2004; *Chem. Abstr*. 2005, *142*, 266815.

15. Jones, P.; Altamura, S.; Boueres, J. K.; Ferrigno, F.; Fonsi, M.; Gavory, G.; Giomini, C.; Lamartina, S.; Monteagudo, E.; Onroria, J. M.; Orsale, M. V.; Roscilli, G.; Rowey, M.; Scarpelli, R.; Schultz-Fademrecht, C.; Toniatti, C. Discovery of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (MK-4827): a novel oral poly(ADP-ribose)polymerase (PARP) inhibitor efficacious in BRCA-1 and -2 mutant tumors. *J. Med.Chem.* **2009**, *52*, 7170-7185.

16. Ruechardt, C.; Hassmann, V. Simplification of the Jacobson indazole-synthesis. *Liebigs Ann. Chem*. **1980**, 908-927.

17. Kunka, C. P. A.; Warkentin, J. Facile 5-endo ring closures to the azo group. A free radical synthesis of indazoles. *Can. J. Chem*. **1990**, *68(4*), 575-580.

18. Reddy, K. R.; Roy, A.; Ila, H.; Junjappa, H. Regiospecific generation and application of 3-lithiomethyl-2-methyl-1-phenylpyrazolin-5-one as 1,3-binucleophile in aromatic annelation: A novel approach for synthesis of 1,2-disubstituted indazolones and their condensed analogs. *Tetrahedron.* **1995**, *51*, 10941-10952.

19. O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev*. **2008**, *37*, 308-319.

20. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev*. **2008**, *37*, 320-330.

21. Petrov, A. V. Fluorinated Heterocyclic Compounds: Synthesis, Chemistry and Applications; John Wiley & Sons: New York, **2009**.

22. Surmont, R.; Verniest, G.; De. Kimpe, N. Structure-Based Design of (5-Arylamino-2*H*-pyrazol-3-yl)-biphenyl-2',4'-diols as Novel and Potent Human CHK1 Inhibitors. *Org. Lett*. **2010**, *12(20),* 4648-4651.

23. Begue, J. P.; Bonnet-Delpon, D. Eds. *Bioorg. and Med. Chemistry of Fluorine*; John Wiley and Sonds, Inc.; NJ **2008.**

24. Revanna.C.N.; Swaroop.T.R.; Raghavendra.G.M.; Bhadregowda.D.G.; Mantelingu.K.; Rangappa.K.S. Practical and Green Protocol for the Synthesis of Substituted 4H-Chromenes Using Room Temperature Ionic Liquid Choline Chloride-Urea. *Journal of Heterocyclic Chemistry*. **2012**, 49, 851-855.

25. Chigalli N. Revanna.; Goravanahalli M. Raghavendra.; Kebbahalli N. Nandeesh.; Bhadregowda.D.G.; Rangappa, K. S.; Kempegowda Mantelingu. Convenient synthesis of novel *N*-(5-allyl-7,7-difluoro)-4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-carboxymides. *Tetrahedron Lett*. **2013**, 54, 5224-5226.

26. Raghavendra, G. M.; Ramesha, A. B.; Revanna, C. N.; Nandeesh, K. N.; Mantelingu, K.; Rangappa, K. S. One-Pot Tandem Approach for the Synthesis of Benzimidazoles and Benzothiazoles from Alcohols. *Tetrahedron Lett*. **2011**, *52,* 5571-5574.