Organic Chemistry: An Indian Journal

Organic Chemistry
ISSN: 0974-7516

Research | Vol 13 Iss 1

8-Fluoro-1-Benzosuberone: An Efficient Key Precursor for Novel Synthesized Poly functionally Fluro Substituted Benzo[b]Cycloheptan-5-one Derivatives as Potential Anti-tumor Agents.

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Received: May 26, 2017; **Accepted:** June 28, 2017; **Published:** June 29, 2017

Abstract

A number of pyrimidine (3a-c), pyrazole (4c-e), pyrane (5a-e), pyridine (6a, b), (9), thiole(7a,b) and ylidine malononitrile derivatives (8) were prepared using 8-fluoro-1-benzosuberone (1) as a starting material. The structures of the novel synthesized products were elucidated based on their microanalyses and spectroscopic data. Finally, the bioactivities of some of the new compounds as antitumor agents against three cell lines of human cancer (breast, colon and prostate) were examined.

***Keywords:** 8-Fluoro-1-benzosuberone ; Pyranes ; Pyrimidines ;Pyridines; Pyrazoles ; Thiophenes; Anti-tumor activity .*

Introduction

Cancer has become most challenging problem and leading cause of death worldwide. Various synthetic and certainly heterocyclic compounds have been reported for their anticancer activity(1- 7,13,16). Therefore, synthesis of compounds with biological anti- cancer interest is the driving force for the discovery and design of new bioactive compounds. Moreover, the biological and medicinal activity of pyranes (4,6-9), pyrimidines(10-12) pyridines(13-16), pyrazoles(17-19) and thioles(20-22) has stimulated considerable interest in the chemistry of these ring systems. In addition, fluorinated compounds are of promising pharmacological activities which are originated from their unique high thermal stabilities and lipophilicity (23). In view of these reports and in continuation of our previous works in heterocyclic chemistry, we have herein synthesized novel heterocyclic ring systems fused with 3-fluoro-6,7,8,9-tetrahydro-5H-benzohepten-5-one (1) in order to evaluate their anti-tumor activities.

Citation: Gad WA. 8-Fluoro-1-Benzosuberone: An Efficient Key Precursor for Novel Synthesized Poly Functionally Fluoro Substituted Benzo [B] Cycloheptan-5-One Derivatives As Potential Anti-Tumor Agents.Org Chem Ind J. 2017;13(1):116

Chemistry

In the present work , 8-Fluoro-1-benzosuberone (1) was condensed with aromatic aldehydes , namely , benzaldehyde , 4-fluoro,3,4-dimethoxy ,4-N,N-dimethylamino ,4-amino and 4-(pyridine-3-yl) benzaldehydes in the presence of alcoholic potassium hydroxide to give the newly synthesized compounds (2a-f) , respectively (Scheme 1) . The structure of compounds (2a-f) was established on the basis of IR and 1 H NMR evidences.

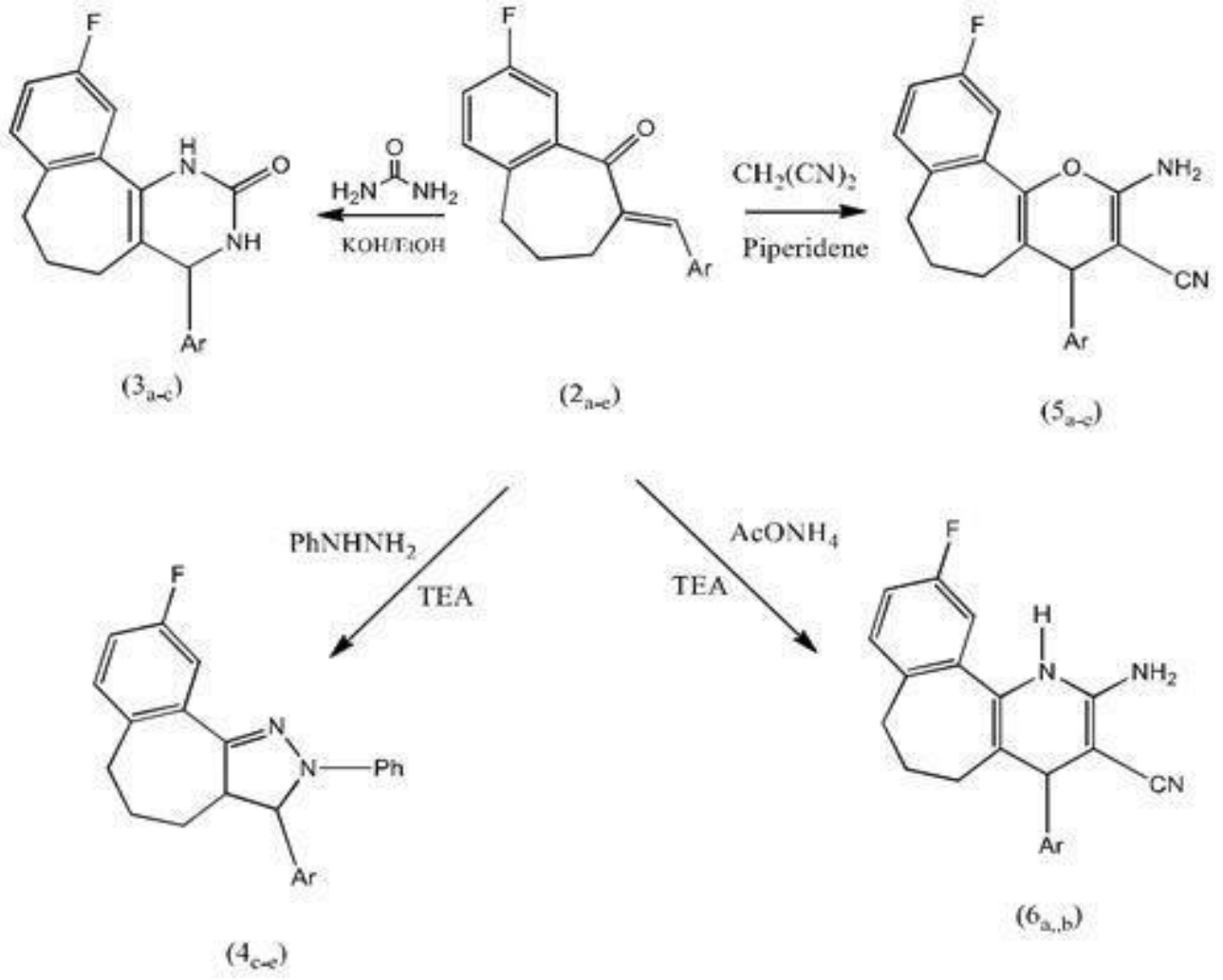
SCHEME 1

(1) (2_{a-f})

a, Ar = Ph ; b,Ar=p-F; c,Ar=3,4-dimethoxy
d, Ar=p-N,N dimethylamino ; e, Ar = p-nitro
f, Ar =p-(pyridin-3-yl)

On refluxing arylmethylene derivatives (2 a-c) with urea in ethanolic potassium hydroxide , pyrimidin-2-one derivatives(3a-c) were obtained . Treatment of compounds (2c-e) with phenylhydrazine and few drops of triethylamine as a catalyst furnished pyrazole derivatives (4c-e) Fused pyrane ring systems (5a-e) were obtained by stirring a solution of arylmethylene derivatives (2 a-e) and malonitrile in absolute ethanol and few drops of piperidine as a catalyst . Reaction of compound (2a,b) with malononitrile and ammonium acetate in the presence of triethyl amine gave the corresponding pyridine-3-carbonitriles (6a,b) (Scheme 2) .

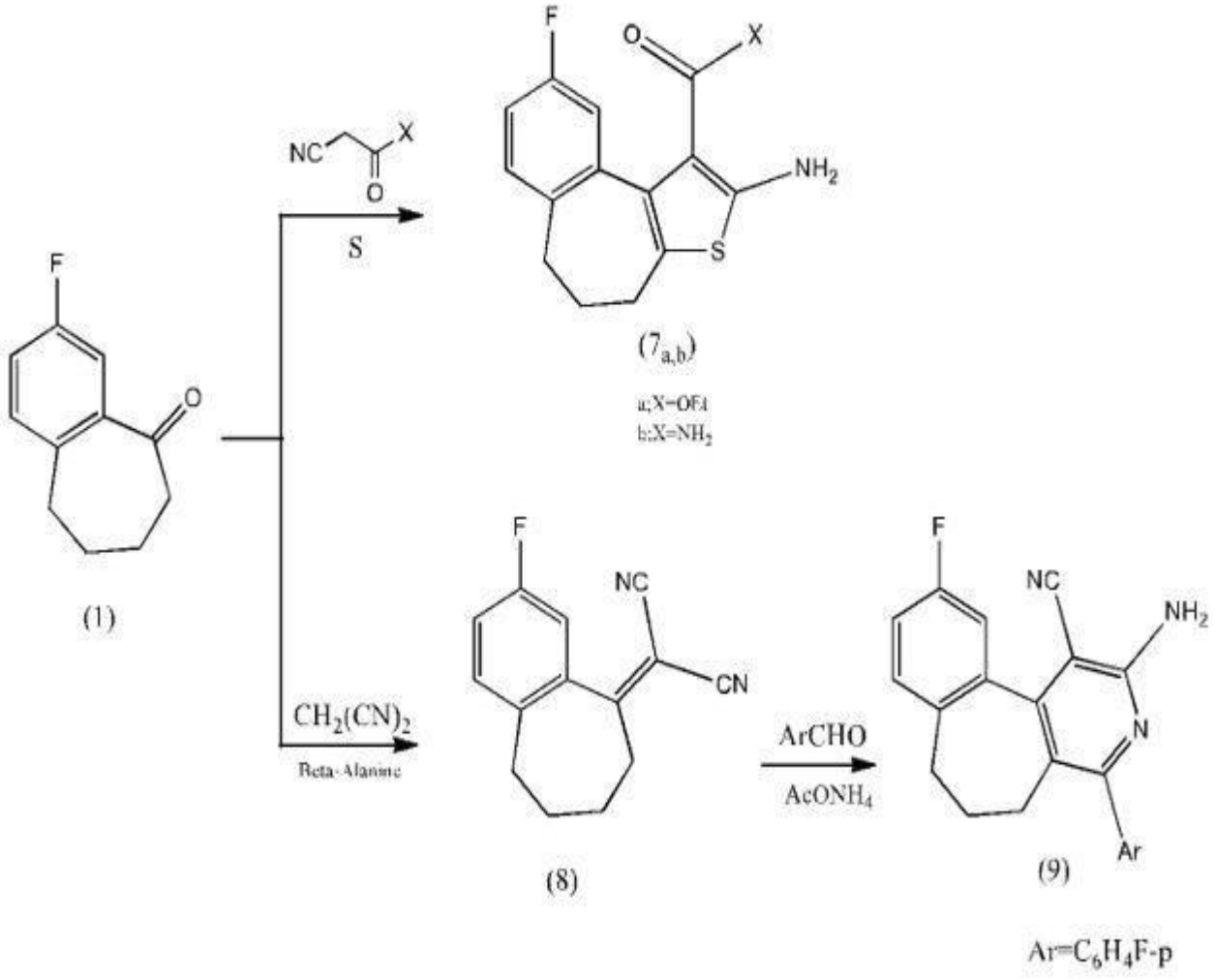
SCHEME 2



a,Ar =Ph ; b,Ar =p-F ; C , Ar=3,4-dimethoxy
d,Ar=p-N,N-dimethylamino ; e,Ar=p-NO_2

On the other hand , 2-Amino- thiophene ester (7a) and 2-amino thiophene carboxamide (7b) were synthesized by condensing cyanonitriles,sulfur powder and 3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (1) in presence of dimethyl amine as a catalyst under Gewald reaction condition(24) .Condensation of compound (1) with malononitrile afforded ylidene malononitrile derivative (8) . Compound (8) was reacted with p-fluorobenzaldehyde and ammonium acetate to afford 2-amino-4-aryl-10-fluoro-6,7-dihydro-5H-benzo[3,4]cyclohepta[1,2-c]pyridine-1-carbonitrile (9) (Scheme3).

SCHEME 3



Biological Screening

Some of the synthesized heterocyclic compounds were screened for their anticancer activity. Each compound was tested at four concentrations against 3 cell lines of human cancer which are breast, colon and prostate cancer. The results expressed as IC50, which the drug concentration (M) is causing a 50% reduction in the net protein increase in control cells during the drug incubation, are collected in TABLE 1. It has been observed through the results obtained from the antitumor test that: 1 Pyrane, pyrazole pyrimidine and pyridine moieties fused to fluorobenzosuberone ring are essential for antitumor activities. 2 Compounds (2b,d),(3b), (5,b-d)are the most active prepared derivatives against breast cell lines.

TABLE 1. ***In vitro*** **tumor cell growth inhibition data against three different tumor/cell lines.**

Panel/cell line				Panel/cell line			
Compd	**Breast cancer MCF7**	**Colon cancer HCT**	**Prostate cancer PC3**	**Compound**	**Breast cancer MCF7**	**Colon cancer HCT**	**Prostate cancer PC3**
2a	7.55	18.2	9.32	4e	14.7	19.6	13.5
2b	3.06	29.3	10.9	5b	4.2	9.92	11.6
2c	12.88	15.89	22.5	5c	4.98	11.76	9.18
2d	4.1	10.9	17.6	5d	4.56	8.8	20.7
2e	17.7	23.2	9.9	6a	16.9	27.3	18.1
3b	5.01	14.2	16.32	6b	15.6	21.9	10.1
3c	18.12	7.54	21.35	7b	12.9	17.13	23.9
4c	16.23	19.6	10.8	9	9.1	11.8	8.78
4d	12.87	30.6	11.1	-	-	-	-

Experimental Section

Melting points were determined on open glass capillaries using an electrothermal I A 9000 digital melting point apparatus and are uncorrected. IR spectra are recoded (KBr) on PyeUnicam SP-1000 instrument spectrophotometer. 1H NMR spectra are obtained on a Varian Mercury VXR -300 MHz spectrometer (CDCl3) using tetramethylsilane (TMS) as an internal reference. Chemical shifts are expressed as (ppm). Mass spectra are recorded on an MS 30 or MS 9 (AEI) mass spectrometer operating at 70 eV . The elemental analyses are formed at Micro Analytical center at Cairo University and the Micro Analytical unit at the National Research Center. Follow up the reactions and checking the purity of the compounds are made by TLC on silica gel precoated aluminum sheets (Type 60 F 254, Merck, Darmstadt, Germany), and the spots are detected by exposure to UV lamp at 365 nm for few seconds. The antitumor activity is evaluated by National Cancer Institute, Cancer Biology Department, Cairo University. All the chemicals purchased from Sigma-Aldrich company, and are used as received without further purification.

6-(Substituted benzylidine)-3-fluoro-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (2a-f)

To a mixture of 8-fluoro-1-benzosuberone (1) (1.78 g, 10 mmol) and aromatic aldehydes, namely, benzaldehyde, p-fluoro, 3,4-dimethoxy, p-N, N-dimethylamino, p-nitro and p-(pyriden-3-yl) benzaldehyde (10 mml), a solution of potassium hydroxide [0.56 g, (10 mmol) in 0.5 ml water] was added in ethanol (10 ml) and the reaction mixture was stirred at room temperature for 1 h. The formed precipitate was filtered off, washed with water, dried and crystallized from the proper solvent to give the corresponding arylmethylene derivatives (2a-f) respectively.

6-Benzylidine-3-fluoro-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (2a)

Yield (92%); m.p.122°C-122.7°C (Ethanol); IR (KBr, cm^{-1}): 1666 (C=O); 1H NMR (CDCl3) 8.1 (s, 1H, =CH proton), 8.00-7.8 (m,3H, Ar H),7.3 (m,5H, Ar H) and 3.1-2.9 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 266 [M^+] (29), 189 [M^+-C_6H_5] (100), 161[189-CO] (71), Anal. Calculated% for $C_{18}H_{15}OF$ 266 (found) C 81.2(81); H 5.64 (5.61); F 7.14 (7.10).

6-(p-Fluorobenzylidine)-3-fluoro-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (2b)

Yield (86%); m.p.107°C-108°C (Ethanol); IR (KBr, cm^{-1}): 1655 (C=O); 1H NMR (CDCl3) 8.4 (s, 1H, =CH proton), 8.5-7.7 (m,3H, Ar H),7.9 (m,5H, Ar H) and 3.3-3.1 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 284 [M^+] (39), 189 [M^+-C_6H_4F] (100), 161[189-CO] (66), Anal. Calculated% for C_{18} $H_{14}OF_2$ 284 (found) C 76.05(75.97); H4.92 (5.01); F 13.38 (13.08).

***6*-(3', 4'-Dimethoxybenzylidine)-3-fluoro-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (2c)**

Yield (79%); m.p.144°C-144.7°C (Ethanol); IR (KBr, cm^{-1}): 1660 (C=O); 1H NMR (CDCl3) 8.6(s, 1H, =CH proton), 8.5-7.8 (m, 3H, Ar H),7.5-7.2 (m,4H, Ar H), 3.5 (s,6H,$2CH_3$) and 3.0-2.3 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 326 [M^+] (31), 189 [M^+-$C_6H_3(OMe)_2$] (73), 161 [189-CO] (100), Anal. Calculated% for $C_{20}H_{19}O_3F$ 326 (found) C 73.62 (73.58); H 5.83 (5.79); F 5.83 (5.72).

6-(p-N, N-Dimethylaminobenzylidine)-3-fluoro-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (2d)

Yield (76%); m.p.174°C-175°C (n-hexane); IR (KBr, cm^{-1}): 1667 (C=O); 1H NMR (CDCl3) 8.2(s, 1H, =CH proton), 8.2-7.8 (m,3H, Ar H),7.5-7.3 (m, 4H, Ar H),2.9(s,6H,$2CH_3$) and 3.2-2.1 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 309 [M^+] (27), 189 [M^+-$C_6H_4NMe_2$] (68), 161 [189-CO] (100), Anal. Calculated% for $C_{20}H_{20}NO$ F 309 (found) C 77.67(77.53); H 6.47 (6.38); F 6.15 (6.1).

6-(p-Nitrobenzylidine)-3-fluoro-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (2e)

Yield (66%); m.p.165°C-166.5°C (Ethanol); IR (KBr, cm^{-1}): 1660 (C=O); 1H NMR (CDCl3) 8.5(s, 1H, =CH proton), 8.3-7.8 (m,3H, Ar H), 7.2-7.5 (m, 4H, Ar H) and 2.9-2.1 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 311 [M^+] (18), 189 [M^+-$C_6H_4NO_2$] (56), 161[189-CO] (100), Anal. Calculated% for $C_{18}H_{14}NO_3$ F 311 (found) C 69.45 (69.41); H 4.5 (4.47); N 4.5 (4.49) F 6.11 (6.1).

6-[(p-Pyridin-3-yl) benzylidine]-3-fluoro-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (2f)

Yield (66%); m.p.184°C-186.5°C (n-hexanel); IR (KBr, cm^{-1}): 1650 (C=O); 1H NMR ($CDCl_3$) 8.6(m, 3H, of pyridine ring)7.7(s, 1H, =CH proton), 7.6-7.2 (m, 4H, Ar H),7.2-7.5 (m, 4H, Ar H) and 3.2-2.9 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 343 [M^+] (15), 265 [M^+-C_5H_4N](22) 189 [M^+-$C_{11}H_8N$](28), 161[189-CO](100), Anal. Calculated% for $C_{23}H_{18}NOF$ 343 (found) C 80.47 (80.44); H 5.25 (5.20); N 4.08 (4.00) F 5.54 (5.52).

Synthesis of 10-fluoro-4-aryl-1, 3, 4, 5, 6, 7hexahydrobenzo-[6, 7] cyclohepta[1,2-d] pyrimidine-2-one derivatives (3a-c) A mixture of (2a-c) (10 mml) and urea (0.6 g, 10 mmol) in ethanolic potassium hydroxide (2 g KOH in 100 ml ethanol) is refluxed for 5 h. The formed precipitate is filtered off, washed with water, dried and crystallized from the proper solvent to give (3a-c), respectively.

10-Fluoro-4-phenyl-1, 3, 4, 5, 6, 7hexahydrobenzo-[6, 7] cyclohepta [1, 2-d] pyrimidine-2-one (3a)

Yield (71%); m.p.171-173°C (ethanol) ; IR (KBr, cm^{-1}) : 3334,3260 (2NH); 1H NMR (DMSO-d6) 9.9, 8.6 (2s, 2 H, 2NH,D2O exchangeable), 8.3.-7.60 (m, 3H, Ar H), 7.3-6.7(m,5H,aromatic)5.2 (s,1H, pyrimidine H)and 3.2-2.1 (m,6H,3CH of cycloheptene ring) ; MS, m/z (%) : 308 [M+] (53), 231 [M+ -C_6H_5] (100), and 212[219-F] (28); Anal Calculated% for $C_{19}H_{17}N_2O$ F 308(found) C 74.03 (73.77); H 5.52 (5.5) ; N 9.09 (9);F 6.17 (6.04).

10-Fluoro-4-(p--fluorophenyl)-1, 3, 4, 5, 6, 7-hexahydrobenzo-[6, 7] cyclohepta [1, 2-d] pyrimidine-2-one (3b)

Yield (83%); m.p 243°C-236°C (Ethanol); IR (KBr, cm^{-1}): 3414,3333 (2NH); 1H NMR ((DMSO-d_6)): 10.1-9.6(2s, 2H, 2NH, D_2O exchangeable), 7.9-7.3(m, 4H, Ar H), 7.7-6.8 (m, 3H, Ar H), 5.10 (s, 1H, pyrimidine H) and 2.9-2.3 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 326 [M^+] (95), 231 [M^+-C_6H_4F] (100) and 212[219-F] (80); Anal. Calculated% for $C_{19}H_{16}N_2OF_2$ 326 (found) C 69.9 (69.85); H 4.9 (4.86); N 8.58 (8.55); F 11.66 (11.65).

10-Fluoro-4-(3, 4-dimethoxyphenyl)-1, 3, 4, 5, 6, 7hexahydrobenzo-[6, 7] cyclohepta [1, 2-d] pyrimidine-2-one (3c)

Yield (89%); m.p 271°C-272°C (Methanol); IR (KBr, cm^{-1}): 3333,3245 (2NH); 1H NMR ((DMSO-d_6): 10.6,9.2(2s, 2H, 2NH, D_2O exchangeable), 8.1-7.7(m, 4H, Ar H),7.6-7.1 (m, 3H, Ar H), 5.2 (s, 1H, pyrimidine H), 3.9(s,6H,$2CH_3$) and 2.9-2 (m, 6H, 3CH2 of cycloheptene ring); MS, m/z (%): 368 [M^+] (80), 231 [M^+-$C_6H3(OMe)_2$] (100) and 212[231-F] (45); Anal. Calculated% for $C_{21}H_{21}N_2O_3F$ 368 (found) C 68.48 (67.65); H 5.71 (5.7); N 7.61 (7.6); F 5.16(5.11).

Synthesis of 3-aryl-9-fluoro-2-phenyl-2, 3, 3, 4, 5, 6hexahydrobenzo-[6, 7] cyclohepta [1, 2-c] pyrazole derivatives (4c-e)

To a mixture of compounds (2c-e) (5mmol) and phenyl hydrazine (0.54 g, 5 mmol) in absolute ethanol (50 ml, few drops of triethylamine (TEA) are added as a catalyst. The reaction mixture is refluxed for 4 h, after cooling; the formed solid is collected by filtration, dried and crystallized from the suitable solvent to give the corresponding pyrazole derivatives (4c-e).

3-(3, 4-Dimethoxyphenyl)-9-fluoro-2-phenyl-2, 3, 3, 4, 5, 6hexahydrobenzo-[6, 7] cyclohepta [1, 2-c] pyrazole (4c)

Yield (78%); m.p. 198°C-200°C (ethanol); IR (KBr, cm^{-1}): 1565 (C=N);1H NMR (C DCl3):7.7-6.9 (m, 11H, Ar H) 4.6-4.5(d, 1Ha, pyrazole H), 4,3-3.35 (m,3H, Hb+CH_2, cycloheptene ring), 3.8(s, 6H, $2CH_3$) and 3.1-1.9 (m, 4H, CH_2, cycloheptene ring); MS, m/z (%): 415 [M^+] (69), 278 [M^+-$C_6H_3(OMe)_2$] (100), 201 [278-C6H5] (50) and 182 [201-F] (41); Anal. Calculated% for $C_{26}H_{24}N_2O_2F$ 415 (found) C 75.18 (75.08); H 5.78 (5.71); N 6.75 (6.70) F 4.57 (4.51).

3-(4-N, N-Dimethylaminophenyl)-9-fluoro-2-phenyl-2, 3, 3, 4, 5, 6hexahydrobenzo-[6, 7] cyclohepta [1, 2-c] pyrazole (4d)

Yield (73%); m.p. 217°C-219°C (ethanol); IR (KBr, cm^{-1}): 1579 (C=N);1H NMR (CDCl3):,7.67-6.2 (m, 12H, Ar H) 4.8 (d, 1Ha,pyrazole H), 4,65-3 (m, 3H, Hb+CH_2, cycloheptene ring), 2.7(s, 6H, $2CH_3$) and 2.9-1.9 (m, 4H, CH_2, cycloheptene ring); MS, m/z (%): 398[M^+] (56), 278[M^+-C6H4N$(Me)_2$] (100), 201 [278-C6H5] (13) and 182 [201-F] (32); Anal. Calculated% for $C_{26}H_{25}N_3F$ 398 (found) C 78.39 (78.29); H6.28 (6.17); N 10.55(10.47) F 4.77 (4.65).

3-(4-Nitrophenyl)-9-fluoro-2-phenyl-2, 3, 3, 4, 5, 6hexahydrobenzo-[6, 7] cyclohepta [1, 2-c] pyrazole (4e)

Yield (63%); m.p. 201°C-203°C (ethanol); IR (KBr, cm^{-1}): 1568 (C=N);1H NMR (CDCl3): 8.1-7 (m, 12H, Ar H) 4.5-4.2 (d, 1Ha, pyrazole H), 4,4-3.6 (m, 3H, Hb+CH_2, cycloheptene ring), and 2.9-1.7 (m, 4H, CH_2, cycloheptene ring); MS, m/z (%): 400 [M^+] (66), 278[M^+-$C_6H_4NO_2$] (100), 201 [278-C_6H_5] (19) and 182 [201-F] (22); Anal. Calculated% for C24H19N3O2 F 400 (found) C 72 (71.8); H 4.75 (4.66); N 10.5 (10.3) F 4.75 (4.71).

Synthesis of 2-amino-4-aryl-10-fluoro-4, 5, 6, 7 tetrahydrobenzo [6, 7] cyclohepta [1, 2-b] pyran-3carbonitrile derivatives (5a-e)

A mixture of compounds (2a-e) (5 mmol), malononitrile (0.33 g, 5mmol) and few drops of piperidine in absolute ethanol (100 ml) is stirred at room temperature for 8 h. The solvent is concentrated under reduced pressure; the formed solid is filtered off, dried and crystallized from the proper solvent to give the corresponding cyanoaminopyrane (5a-e), respectively.

2-Amino-4-phenyl-10-fluoro-4, 5, 6, 7 tetrahydrobenzo [6, 7] cyclohepta [1, 2-b] pyran-3carbonitrile (5a)

Yield (58%); m.p. 228°C-229°C (Ethanol); IR (KBr, cm^{-1}): 3400, 3370 (NH_2) and 2220 (CN); 1H NMR (CDCl3): 7.4-6.9 (m, 3H, Ar H), 6.3 (m, 3H, Ar H),4.1 (s, 2H, NH_2), 3.9 (s, 1H, pyrane proton), and 2.8-2.3 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 332[M^+] (46), 255 [M^+-C_6H_5] (72), 213 [255-NH_2, CN] (100), 194[213-F] (13); Anal. Calculated% for $C_{21}H_{17}N_2OF$ 332 (found) C 75.09 (75.06); H 5.12 (4.09); N 8.4 (8.28); F 5.72 (5.66).

2-Amino-4-(p-fluorophenyl)-10-fluoro-4, 5, 6, 7 tetrahydrobenzo [6, 7] cyclohepta [1, 2-b] pyran-3carbonitrile (5b)

Yield (61%); m.p. 241°C-242°C (Ethanol); IR (KBr, cm^{-1}): 3380, 3365 (NH_2) and 2220 (CN); 1H NMR (CDCl3): 7.1-6.8 (m, 3H, Ar H), 6.4 (m, 3H, Ar H),4 (s, 2H, NH_2), 4.6 (s, 1H, pyrane proton), and 2.6-1.7 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 350[M^+] (61), 255 [M^+-C_6H_5F] (55), 213 [255-NH_2, CN] (100), 194[213-F] (18); Anal. Calculated% for $C_{21}H_{16}N_2OF$ 2350 (found) C 72 (71.8); H 4.57 (4.47); N 8 (7.6); F 10.86 (10.6).

2-Amino-4-(3', 4'-dimethoxyphenyl)-10-fluoro-4, 5, 6, 7 tetrahydrobenzo [6, 7] cyclohepta [1, 2-b] pyran-3carbonitrile (5c)

Yield (77%); m.p. 273°C-275°C (Methanol); IR (KBr, cm^{-1}): 3443, 3385 (NH_2) and 2218 (CN); 1H NMR (CDCl3): 7.6-6.8 (m, 3H, Ar H), 6.1 (m, 3H, Ar H),3.9 (s, 2H, NH_2), 3.9 (s, 1H, pyrane proton), 3.9(s,6H,2CH_3) and 3-2.8 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 392[M^+] (46), 255 [M^+-$C_6H_3(OMe)_2$] (81), 213 [255-NH_2, CN] (100), 194[213-F] (19); Anal. Calculated% for $C_{23}H_{21}N_2O_3F$ 392 (found) C 70.41 (70.34); H 5.36 (5.28); N 7.14 (7.03); F 4.85 (4.71).

2-Amino-4-[(p-dimethylamino) phenyl]-10-fluoro-4, 5, 6, 7 tetrahydrobenzo [6, 7] cyclohepta [1, 2-b] pyran-3carbonitrile (5d) Yield (71%); m.p. 256°C-258°C (Ethanol); IR (KBr, cm^{-1}): 3444, 3390 (NH_2) and 2222 (CN); 1H NMR (CDCl3): 7.6-6.7 (m, 3H, Ar H), 6.4 (m, 3H, Ar H),3.6 (s, 2H, NH2), 4.1 (s, 1H, pyrane proton), 3(s,6H,2CH_3) and 2.7-2 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 375[M^+] (36), 255 [M^+-C6H4N$(Me)_2$] (55), 213 [255-NH_2, CN] (100), 194[213-F] (25); Anal. Calculated% for $C_{23}H_{22}N_3OF$ 375 (found) C 73.6(73.45); H 5.88 (5.87); N 11.2 (11.04); F 5.07 (5.05).

2-Amino-4-(p-Nitrophenyl-10-fluoro-4, 5, 6, 7 tetrahydrobenzo [6, 7] cyclohepta [1, 2-b] pyran-3carbonitrile (5d)

Yield (48%); m.p. 205°C-206°C (Ethanol); IR (KBr, cm^{-1}): 3433, 3380(NH_2) and 2222 (CN); 1H NMR (CDCl3): 7.8-6.7 (m, 3H, Ar H), 6.1 (m, 3H, Ar H), 3.1 (s, 2H, NH_2), 4.2 (s, 1H, pyrane proton), and 2.7-2 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%): 377[M^+] (68), 255 [M^+-C6H4NO_2] (49), 213 [255-NH_2, CN] (100), 194[213-F] (19); Anal. Calculated% for $C_{21}H_{16}N_3O_3F$ 377 (found) C 66.84(66.8); H 4.24 (4.19); N 11.14 (11.1); F 5.04 (5.01).

Synthesis of 2-Amino-4-aryl-10-fluoro-l-2, 3, 3, 4, 5, 6hexahydrobenzo-[6, 7] cyclohepta [1, 2-b] pyridine-3-carbonitrile derivatives (6a,b)

A few drops were added to a mixture of ($2_{a, b}$) (10mmol), malononitrile (0.66 g, 10 mmol) and ammonium acetate (3.85 g, 50 mmol) in absolute alcohol (40 ml) was refluxed for 6 h. The reaction mixture was cooled and poured onto cold water. The solid formed was filtered off, washed with water, dried and crystallized from the proper solvent to obtain ($6_{a, b}$).

2-Amino-4-phenyl-10-fluoro-l-2, 3, 3, 4, 5, 6hexahydrobenzo-[6, 7] cyclohepta [1, 2-b] pyridine-3-carbonitrile (6a)

Yield (59%); m.p. 132°C-133°C (Ethanol); IR (KBr, cm^{-1}): 3380, 3310 (NH_2) and 2211 (CN); 1H NMR (DMSO-d_6): 8.3-8 (m, 3H, Ar H), 7.6-72 (m, 3H, Ar H),4.4 (s, 2H, NH_2, exchangeable with D_2O), and 2.3-2 (m, 6H, 3CH2 of cycloheptene ring); MS, m/z (%): 331[M^+] (38), 254[M^+-C_6H_5] (71), 212 [254-NH_2, CN] (100), 193[212-F] (19); Anal. Calculated% for $C_{21}H_{18}N_3$ F 331 (found) C 76.13(76.08); H 5.44 (5.19); N 12.69 (12.61); F 5.74 (5.71).

2-Amino-4-(p-fluorophenyl-10-fluoro-l-2, 3, 3, 4, 5, 6hexahydrobenzo-[6, 7] cyclohepta [1, 2-b] pyridine-3-carbonitrile (6b)

Yield (62%); m.p. 160°C-162°C (Ethanol); IR (KBr, cm^{-1}): 3443, 3380(NH_2) and 2218 (CN); 1H NMR (DMSO-d_6): 8.5-8.2 (m, 3H, Ar H), 7.6-7.1 (m, 3H, Ar H),4.1 (s, 2H, NH2, exchangeable with D_2O), and 2.6-2.1 (m, 6H, 3CH2 of cycloheptene ring); MS, m/z (%): 349[M^+] (21), 254[M^+-C_6H_4F] (88), 212 [254-NH_2, CN] (100), 193[212-F] (24); Anal. Calculated% for $C_{21}H_{17}N_3F_2$ 349 (found) C 72.21(72.17); H 4.87 (4.81); N 12.03 (12.01); F 10.89 (10.88).

Synthesis of 2-amino-5-fluoro, 8, 9-dihydro-5H-benzo [3, 4] cyclohepta [1, 2-b] thiophen-3-ethyl carboxylate (7_a)

An equimolar mixture of powdered sulfur (0.064 g, 2 mmol) and diethyl amine (DEA) (0.146 g, 2 mmol) was stirred until total dissolution of the sulfur. After, the ethyl cyanoacetate (0.226 g, 2mmol) and 3-fluoro-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (1) (0.356 g, 2 mmol) were added to the reaction mixture, which was stirred at room temperature for 3 h. After completion of the reaction, as monitored by TLC, the crude product was filtered off, dried and crystallized to yield the desired product. Yield (71%); m.p. 96°C-10°C (n-hexane); IR (KBr, cm^{-1}): 3433, 3390(NH_2) and 1740 (C=O); 1H NMR (CDCl3): 9.8(s,2H,NH2), 7.8-7.1 (m, 3H, Ar H),3.6-2.8 (q, 2H, CH2), 2.5-2.1 (m, 6H, 3CH2 of cycloheptene ring) and 1.9-1.1(t, 3H, CH3); MS, m/z (%): 305[M^+] (48), 260[M^+-OEt] (100); Anal. Calculated% for $C_{16}H_{16}NO_2SF$ 305 (found) C 62.95 (62.88); H 5.25 (5.11); N 4.59 (4.56); S 10.49 (10.41) F 6.23 (6.21).

Synthesis of 2-amino-5-fluoro, 8, 9-dihydro-5H-benzo [3, 4] cyclohepta [1, 2-b] thiophen-3-carboxamide (7_b)

A mixture of cyanoacetamide (0.168 g, 2mmol), 3-fluoro-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (1) (0.356 g, 2 mmol), sulfur powder (0.064 g, 2 mmol), in ethanol (5 ml) was stirred at room temperature,diethyl amine (DEA) was added dropwise until complete dissolution of sulfur. The reaction mixture was left overnight in refrigerator. The obtained precipitate

was filtered off, dried and recrystallized from ethanol Yield (58%); m.p. 177°C-179°C (Ethanol); IR (KBr, cm^{-1}): 3400, 3380 (NH_2) and 1655 (C=O); 1H NMR CDCl3): 9.6(s, 2H,NH_2), 7.8 (s, 2H, NH_2), 7.5-6.6 (m, 3H, Ar H), 2.6-2 (m, 6H, 3CH2 of cycloheptene ring); MS, m/z (%): 276[M^+] (65), 24[M^+-2NH_2] (100);Anal. Calculated% for $C_{14}H_{13}N_2OSF$ 276 (found) C 60.87 (60.83); H 4.71 (4.69); N 10.14 (10.01); S 11.59 (11.46) F 6.88 (6.80).

Synthesis of 3-fluoro-l-2, 3, 3, 4, 5, 6hexahydrobenzo-[6, 7] cyclohepta-5H-ylidene malononitrile(8)

A mixture of 3-fluoro-6, 7, 8, 9-tetrahydro-5H-benzocyclohepten-5-one (1) (0.534 g, 3 mmol), malononitrile (0.198 g, 3 mmol), and β-alanine (10 mg) as catalyst in ethanol (10 ml) was refluxed for 4 h. After cooling, the formed product was filtered off, dried and crystallized to afford compound (7) in 77% yield; mp 95°C-96°C (ethanol); IR (KBr, cm^{-1}): 2221 (CN); 1H NMR (CDCl3): 7.7-7.1 (m, 3H, Ar H), and 3.1-2.9 (m, 6H, 3CH2 of cycloheptene ring); MS, m/z (%): 226[M^+] (100), 200[M^+-CN]; Anal. Calculated% for C14$H_{11}N_2F$ 226 (found) C 74.3(74.1); H 4.87 (4.77); N 12.39 (12.21); F 8.4 (8.2).

Synthesis of 2-amino-4-(p-fluorophenyl) 10-fluoro, 6, 7-dihydro-5H-benzo [3, 4] cyclohepta [1,2-c] pyridine-1-carbonitrile (9)

A mixture of product (7) (3 mmol, 0.678 g), p-fluorobenzaldehyde (3 mmol, 0.372 g) and ammonium acetate (8 mmol, 0.616 g) in glacial acetic acid (30 ml) was refluxed for 4h. The reaction mixture was cooled, poured onto ice-water; the formed precipitate was filtered off, dried and crystallized from methanol to give pyridine derivative (9). Yield (67%); m.p. 161°C-163°C (MeOH), IR (KBr, cm^{-1}): 3380, 3320(NH_2) and 2220 (CN); 1H NMR CDCl3): 7.9-6.4 (m, 7H, Ar H), 2.4-1.9 (m, 6H, 3CH_2 of cycloheptene ring), 4.1 (s, 2H, NH_2),; MS, m/z (%): 347[M^+] (28), 309 [M^+-2F] (33), 252[M^+-C_6H_4F] (100); Anal. Calculated% for $C_{21}H_{15}N_3F_2$ 347 (found) C 72.6 (71.81); H 4.32 (4.28); N 12.1 (12.06); F 11.2 (10.89).

Conclusion

Starting material (1) and aryl methylene derivatives (2) are used as precursor for the synthesis of a variety of heterocyclic ring systems formed upon reaction with cyanonitriles and sulfur powder malononitrile, urea, phenyl hydrazine, and ammonium acetate to afford heterocyclic derivatives with expected high biological activity as antitumor agents. Simple methods have been used for preparing substituted fused heterocyclic compounds with multiple functional groups.

Acknowledgements

The author thanks the Deanship of Scientific Research of Taibah University for funding this research project. Thanks and gratitude is expressed to Cairo University, National Cancer Institute and National Research Center, Giza, Egypt for facilities provided during this project.

REFERENCES

1. Andrus PK, Fleck TJ, Hallet ED, et al. Neuroprotective effects of the novel brain-penetrating pyrrolopyrimidine antioxidants U-101033E and U-104067F against post-ischemic degeneration of nigrostriatal neurons. J Neurosci Res. 1997;47(6):650-54.
2. Grivsky EM, Shuliang Lee, Sigel CW. Synthesis and antitumor activity of 2, 4-diamino-6-(2, 5-dimethoxybenzyl)-5-methylpyrido [2, 3-d] pyrimidine. J Med Chem. 1980;23(3):32729.

3. Katritzky AR, Rees CW. Comperhensive Heterocyclic Chemistry. J Heterocyclic Chem.1984;3:129-61.
4. Hammam AG, Fahmy AFM, Amr AE. Synthesis of novel tricyclic heterocyclic compounds as potential anticancer agents using chromanone and thiochromanone as synthons. Indian J Chem. 2003;34(47).
5. Ghalia MA, Amr A. Synthesis and investigation of a new cyclo (N?-dipicolinoyl) pentapeptide of a breast and CNS cytotoxic activity and an ionophoric specificity. Amino acids. 2003;26(3):283.
6. Gad WA, Nassar DO. The utility of 8-Fluoro-1-Benzosuberone in synthesis of newly; Azole, pyrane and pyrimidine derivatives as cytotoxic and anti-tumor agents. Org Chem An Indian J. 2014;10(10),398-405.
7. Ragab NM, Kheieldin NY, Fahmy AF. Der Pharma Chemica. 2010;2(1)400-417.
8. Abdou WM, Ganoub NA, Fahmy AF, et al. Synthetic studies using unsaturated and active phosphonium salts. A convenient preparation of furano-and pyrano [2,3-c] pyridazines and substituted quinolines. Heteroatom Chemistry. 2005;16(1):56-64.
9. Abdelrazek FM, Metz P, Metwally NH. Synthesis and molluscicidal activity of new cinnoline and pyrano [2, 3-c] pyrazole Derivatives. Arch Pharm. 2006;339(8):456-60.
10. Nasr MN, Gineinah MM. Pyrido [2, 3-d] pyrimidines and Pyrimido [5′, 4′:5, 6] pyrido[2, 3-d] pyrimidines as new antiviral agents: Synthesis and biological activity. Arch Pharm. 2002;335(6):289.
11. Ahulwalia VK, Garg VK, Dahiya A. ChemInform Abstract: A Convenient Synthesis of 6-Ethoxycarbonyl-4-oxo-1, 2, 3, 4-tetrahydro-7H-pyrano (2, 3-d)pyrimidin-7-ones. ChemInform. 2010;26 (21).
12. Gad GA, Al-Harbi HD. Microwave-assisted synthesis of pyrido [4, 3-d] pyrimidine derivatives and their biological evaluation. Org Chem An Indian J 2014;10(12).
13. Sirisha B, Narsaiah B, Yakaiah T, et al. Synthesis and theoretical studies on energetics of novel N-and O-perfluoroalkyl triazole tagged thienopyrimidines: Their potential as adenosine receptor ligands. Eur Med Chem. 2010;45(5):1739-745.
14. Piper JR, McCaleb JS, Montgomery JA. A synthetic approach to poly (gamma-glutamyl) conjugates of methotrexate. J Med Chem. 1983;26(2):291-94.
15. Jiang JB, Hesson DP, Dusak BA, et al. Synthesis and biological evaluation of 2-styrylquinazolin-4(3H)-ones, a new class of antimitotic anticancer agents which inhibit tubulin polymerization. J Med Chem. 1990;33(6):1721-728.
16. Mandeville JP, Descôteaux C, Mandal SK, et al. Synthesis of 17β-estradiol-platinum (II) hybrid molecules showing cytotoxic activity on breast cancer cell lines. Bioorg Med Chem Lett. 2008;18(7):2282-287.
17. Zhang X. J Med Chem. 2008;61:7099-7110.
18. Tavares FX, Boucheron JA, Dickerson SH, et al. N-Phenyl-4-pyrazolo [1, 5-b] pyridazin-3-ylpyrimidin-2-amines as potent and selective inhibitors of glycogen synthase kinase 3 with good cellular efficacy. J Med Chem. 200;47(19):4716-730.
19. Stevens KL, Jung DK, Alberti MJ, et al. Pyrazolo [1, 5-a] pyridines as p38 Kinase Inhibitors. Org Lett. 2005;7(21):4753-756.
20. Sabnis RW, Rangnekar DW, Sonawane ND, et al. 2-aminothiophenes by the gewald reaction. J Heterocycl Chem. 1999;36(2):333-45.
21. Wang W, Shangguan S, Qiu N, et al. Design, synthesis and biological evaluation of novel 3,4,5-trisubstituted aminothiophenes as inhibitors of p53-MDM2 interaction. Part 1. Bio org Med Chem. 2013;21(11):2879-885.

22. Puterová Z, Romiszewski J, Mieczkowski J, et al. Synthesis and study of new rod-like mesogens containing 2-aminothiophene unit. Tetrahedron. 2012;68(39):8172-180.
23. Haga T, Fujikawa K, Koyanagi T, et al. Some New 2-Substituted 5-Trifluoromethylpyridines. Heterocycles. 1984;22(1):117.
24. Gewald K. Zur Reaktion von α-Oxo-mercaptanen mit Nitrilen. Angew Chem. 1961;73(3):114.