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The utility of 8- Fluoro -1- Benzosuberone in synthesis of newly; Azole, pyrane and pyrimidine derivatives as cytotoxic and anti- tumor agents

W.A.Gad*, D.O.Nassar

Department of Chemistry, faculty of Science, Taibah University, (SAUDI ARABIA)

E-mail: wafaagad@gmail.com

ABSTRACT

On condensation 8- fluoro-1-benzosuberone **(1)** with heterocyclic aldehydes affords the corresponding 2-arylidene -1-benzosuberones **(2)** which on treatment with malononitrile and phenylhydrazine yields the cyanoaminopyrane and pyrazole derivatives **(3)** and **(4)**, respectively. Moreover, treatment of the aryl methylene **(2)** with thiourea gives the corresponding thioxopyrimidine derivatives **(5)**, while using urea and guanidine hydrochloride at the similar experimental conditions leads to pyrimidinone and aminopyrimidine derivatives **(6)** and **(7)**, respectively. Some of the discussed compounds show *in vitro* antitumor activity utilizing three human tumor cell lines, representing breast, colon as well as prostate.

KEYWORDS

Fluorobenzosuberone;
Azoles;
Pyranes;
Pyrimidines;
Antitumor activity.

INTRODUCTION

Cancer, the uncontrolled, rapid and pathological proliferation of abnormal cells is the leading cause of human death, after cardiovascular diseases[1]. 7.6 million cancer deaths occurred in the 2008 worldwide and cancer related deaths are estimated to reach 12 million worldwide, by the year of 2015.

Despite considerable progress in the understanding of its biology and pharmacology, cancer remains a serious health problem. Although there has been increasing sophistication of conventional therapeutic strategies, such as surgery, radiotherapy and chemotherapy, such approaches are capable of remediating approximately half of cancer patients, while over 40% of patients arestilllikelydiefromthedisease[1]. Therefore, the search of potent, safe, and selective anti-cancer compounds is a crucial aspect of modern cancer research.

On the other hand heterocyclic compounds are of particular interest due to their unique properties. The biological significance of these molecules has been extensively reported[2 – 17]. Some of these compounds have been shown to exhibit varying biological actions[2-17] making further investigation of their clinical potential, essential.

In view of these information, we would like in this study to synthesis new types, to our knowledge, of bioactive 6 – arylidene 3- fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one using 8-fluoro-1-benzosuberone. The newly prepared 6-arylidene-3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one is utilized as a precursor for the synthesis of different fused pyrimidine, pyrane, and azole derivatives. The bioactivities of the novel compounds are evaluated.

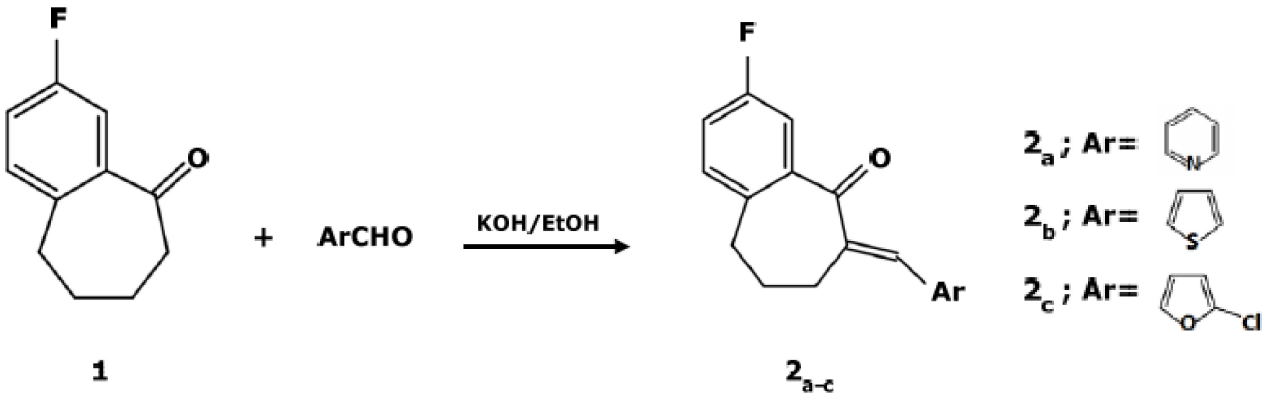
RESULTS AND DISCUSSION

Chemistry

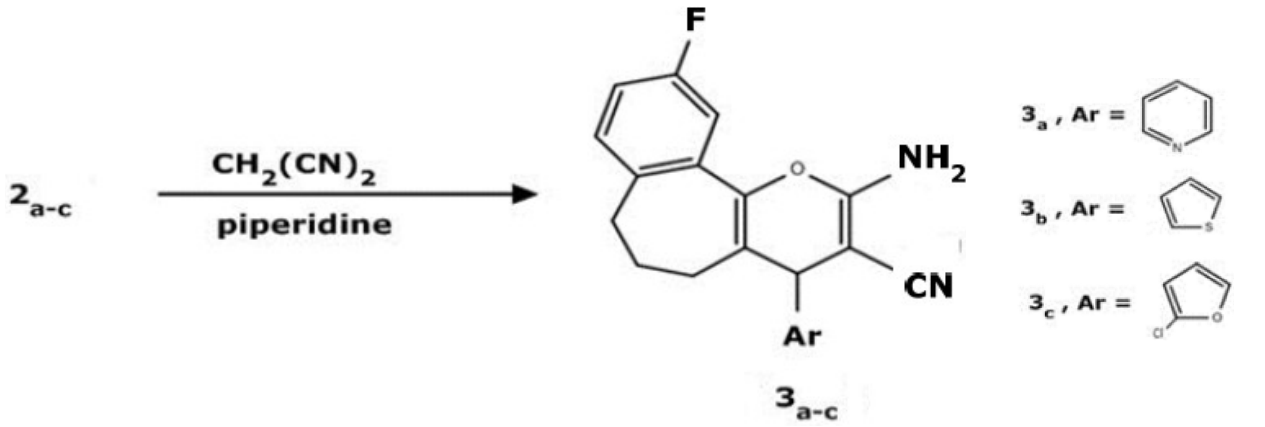
In the present study, we are going to discuss the reaction of 8- fluoro-1-benzosuberone **(1)** with heterocyclic aldehydes, namely, pyridine -4-caboxaldehyde, thiophene-3- carboxaldehyde and 5-chloro-2- furan caboxaldehyde. On stirring compound **(1)** with pyridine -4- aldehyde in alcoholic potassium hydroxide at room temperature, a Knoevenagel type condensed product **(2_a)** is obtained having the molecular formula $C_{17}H_{14}NOF$. The structure of the corresponding 4- pyridinylmethylene derivative **(2_a)** (Scheme 1) is established on the basis of elemental analyses and spectral data.

Under the same experimental conditions, compound **(1)** reacts with thiophene -3-aldehyde and 5-chloro-furan-2-aldehyde to yield the corresponding 3- thienyl and 5-chloro-2- furyl methylene derivatives **(2_b)** and **(2_c)**, respectively (Scheme 1). The structure of compounds **($2_{b,c}$)** was established on the basis of IR and ^{1}H NMR evidences.

As previously reported[18] aryl methylene derivatives can be used as potential precursors for fused heterocyclic systems. Thus, on refluxing compounds **(2_{a-c})** with malononitrile in boiling ethanol in the presence of catalytic amount of piperidine, the condensed products **(3_{a-c})** are obtained (Scheme 2). The condensation of compounds **(2_{a-c})** with malononitrile proceeds via Michael



Scheme 1

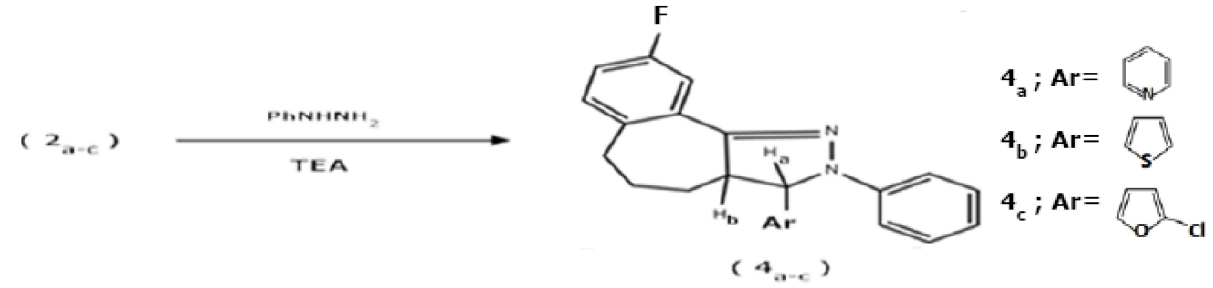


Scheme 2

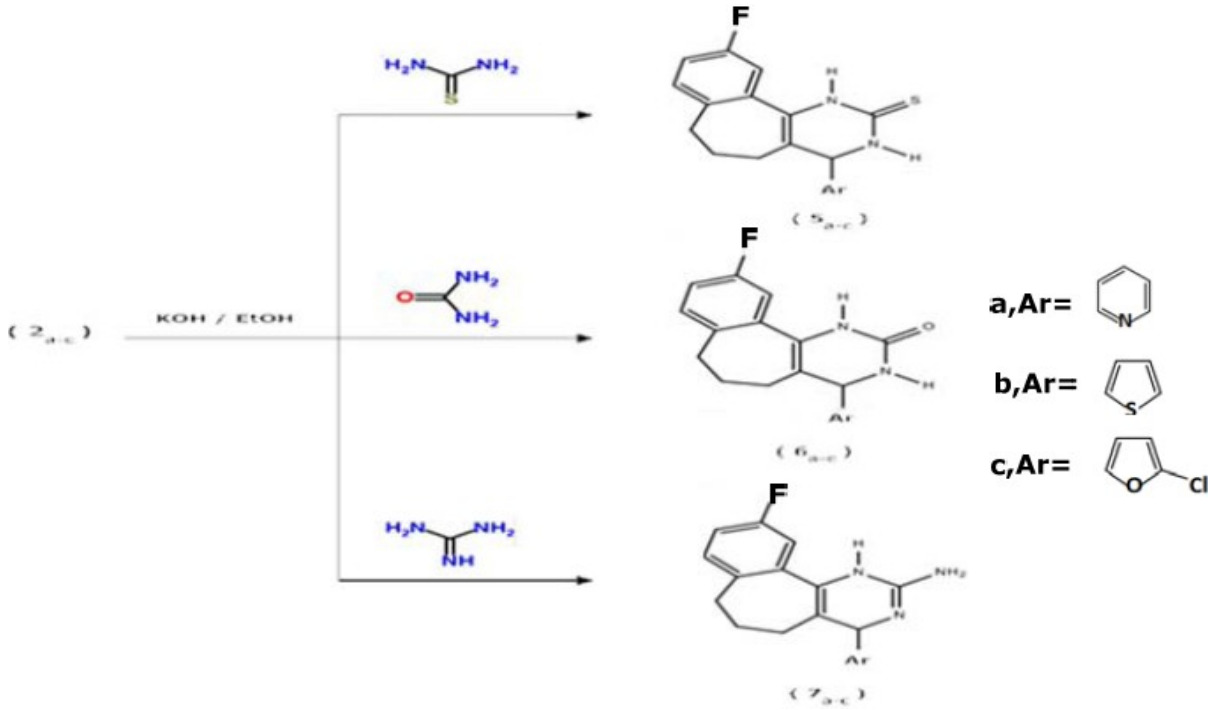
addition reaction to afford the desired products **(3_{a-c})**. The IR spectra of the products reveal (NH_2) absorption band at 3420-3380 cm^{-1} and at 2210 cm^{-1} for (CN) group.

Compounds **(3_{a-c})** are converted to pyrazole derivatives **(4_{a-c})** when refluxed with phenyl hydrazine in absolute ethanol using triethylamine (TEA) as a catalyst (Scheme 3). The IR spectra of the products **(3_{a-c})** show peak at 1598 cm^{-1} for (C=N).

Compounds **(2_{a-c})** are condensed with thiourea in refluxing ethanolic potassium hydroxide to yield the corresponding pyrimidine -2- thiones **(5_{a-c})** (scheme 4). Compounds **(5_{a-c})** reveal IR absorption bands at 3434, 3259 cm^{-1} for (2NH).



Scheme 3



Scheme 4

On heating compounds **(2_{a-c})** under reflux with urea in ethanolic potassium hydroxide, the corresponding pyrimidine -2- ones **(6_{a-c})** are produced (Scheme 4). The IR spectrum of adduct **(6_{a-c})** reveal absorption bands at 1720-1725, 3434 and 3259 cm^{-1} for (C=O) and (2NH), respectively.

Refluxing a mixture of **(2_{a-c})** and guanidine hydrochloride in ethanolic potassium hydroxide affords the corresponding 2- aminopyrimidine derivatives **(7_{a-c})**, respectively (Scheme 4). The IR spectra of compounds **(7_{a-c})** show two absorption bands at 3380 and 3345 cm^{-1} for (NH) and (NH_2), respectively.

Biological screening

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 IC_{50}, 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 and pyrimidine moieties fused to fluorobenzosuberone ring are essential for antitumor activities.
2 Compounds **(2_a)**, **(3_{a-c})**, **($5_{a,b}$)**, and **(7_{a-c})** are the most active prepared derivatives against breast cell lines.
3 The presence of nitrogen heterocyclic rings enhance the reactivity.

EXPERIMENTAL SECTION

Melting points were determined on open glass capil-

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

Compd	Panel / cell line			Compd	Panel / cell line		
	Breast Cancer MCF7	Colon Cancer HCT	Prostate Cancer PC3		Breast Cancer MCF7	Colon Cancer HCT	Prostate Cancer PC3
2_a	3.98	21.5	12.5	5_a	4.6	9.78	11.8
2_b	9.38	28.7	21.4	5_b	4.73	10.6	17.4
2_c	10.1	17.6	19.9	5_c	6.86	8.4	11.05
3_a	3.23	8.03	9.53	6_a	14.08	5.78	15.08
3_b	3.98	8.78	10.4	6_b	18.7	6.9	23.77
3_c	4.18	6.4	9.89	6_c	20.3	4.43	21.4
4_a	13.7	14	11.6	7_a	3.89	11.76	15.07
4_b	14	33.7	14.8	7_b	4.43	13.9	14
4_c	16.8	12.9	10.8	7_c	4.9	10.8	12.59

laries using an electrothermal I A 9000 digital melting point apparatus and are uncorrected. IR spectra are recoded (KBr) on PyeUnicam SP-1000 instrument spectrophotometer. ^{1}H NMR spectra are obtained on a Varian Mercury VXR -300 MHz spectrometer ($CDCl_3$) using tetramethylsilane (TMS) as an internal reference. Chemical shifts are expressed as δ (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 CairoUniversity and the MicroAnalytical 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 λ_{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 furtherpurification.

Synthesis of 6-arylidine-3-fluoro-6,7,8,9-tetrahydro-5H- benzocyclohepten-5-ones (2_{a-c})

To a mixture of 8-fluoro-1-benzosuberone **(1)** (1.78 g, 10mmol) and heterocyclic aldehydes, namely, 3-thiophenecarboxaldehyde, 5-chloro- 2- furan carboxaldehyde and 4- pyridine carboxaldehyde (10mml), a solution of potassium hydroxide [0.56 g, (10mmol) in 0.5 ml water] was added in ethanol (5ml) 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 **(2_{a-c})** respectively.

6- (4-Pyridinylmethylene) -3-fluoro- 6,7,8,9-tetrahydro-5H- benzocyclohepten-5-one (2_a)

Yield (83.89 %); m.p.128.5-129.3 ºC (n- hexane); IR (KBr, cm^{-1}) : 1661 (C=O); ^{1}H NMR ($CDCl_3$) δ :8.70(d, 2H, of pyridine ring), 7.70 (d, 2H, of pyridine ring), 7.50 (s, 1H,=CH proton), 7.5-7.1 (m,3H, Ar–H), and 2.9- 2 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%) : 267 [M^+] (38), 189 [M^+ -C_5H_4N](100), 239[M^+ -CO](82), 170[189-F] (51). Anal. Calcd% for $C_{17}H_{14}NOF$ 267 (found) C 76.40(76.35); H5.24(5.20); N5.24(5.19); F7.12 (7.13).

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

Yield (81.48%); m.p. 150.3-151 ºC(ethanol); IR (KBr, cm^{-1}) : 1655 (C=O); ^{1}H NMR ($CDCl_3$) δ : 7.80(s,1H, of thiophene ring)7.6-7.4 (2d, 2H, of thiophene ring), 7.50 (s,1H, =CH proton),7.3-7.1(m,3H, Ar–H), and 2.9- 1.5 (m, 6H, $3CH_2$ of cycloheptene ring).MS, m/z (%) : 272 [M^+] (100), 189 [M^+ -C_4H_3S] (67), 244 [M^+ -CO] (19), 17O[189 -F] (45). Anal. Calcd% for$C_{16}H_{13}SOF$ 272 (found) C 70.59 (76.35); H4.78 (4.70); S 11.76 (11.73); F 6.99 (6.89)

6- (5-Chloro- 2-furylmethylene)-3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (2_c)

Yield (93.8%); m.p. 120.1-121.4 ºC(n-hexane); IR (KBr, cm^{-1}) : 1660 (C=O). ^{1}H NMR ($CDCl_3$) δ : 6.60-6.30 (2d, 2H, of furan ring), 7.20 (s,1H,=CH

proton), 7.3-7.1 (m, 3H, Ar –H), and 2.8- 2 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%) : 290.5 [M^+] (76), 231.5 [M^+-CO](35), 189 [M^+ -C_4H_2OCl](100), 170 [189 -F] (28). Anal.Calcd %for $C_{16}H_{12}O_2$ F Cl 290.5 (found) C 66.09 (66); H4.13 (4.12); F6.45 (6.40); Cl12.20 (12.18).

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

A mixture of compounds **(2_{a-c})** (5 mmol), malononitrile (0.33g, 5mmol) and few drops of piperidine in absolute ethanol (100ml) is stirred at room temperature for 5 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 **(3_{a-c})**, respectively.

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

Yield (65%); m.p. 223.1 - 224.5º C(benzene); IR (KBr, cm^{-1}) : 3420, 3380 (NH_2) and 2210 (CN); ^{1}H NMR ($CDCl_3$) δ: 8.64-8.62 (d, 2H,of pyridine protons), 7.439-7.38(d, 2H,of pyridine protons), 7.37-6.69 (m, 3H, Ar –H), 4.8 (s, 2H, NH_2), 4.2 (s, 1H, pyrane proton), and 2.6-1.5 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%) : 333[M^+] (61), 255 [M^+ -C_5H_4N] (87), 213 [255 -NH_2, CN] (100), 194[213–F] (24); Anal. Calcd% for $C_{20}H_{16}N_3O$ F 333 (found) C 72.07 (72.03); H4.80 (4.80); N 12.61 (12.58); F 5.71 (5.67).

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

Yield (83%); m.p. 134.5 – 135.2 ºC (pet. ether 60-80ºC); IR (KBr, cm^{-1}) : 3480, 3390 (NH_2) and 2220 (CN); ^{1}H NMR ($CDCl_3$) δ : 7.33 (s, 1H, of thiophene protons), 7.32(d, 1H, of thiophene protons), 7.30 (d, 1H, of thiophene protons), 7.2-6.9(m, 3H, Ar–H), 4.5 (s, 2H, NH_2), 4.3 (s, 1H, pyrane proton),and 2.5- 1.6 (m, 6H, $3CH_2$ of cycloheptene ring) ; MS, m/z (%) : 338 [M^+] (55), 255 [M^+ -C_4H_3S] (69),213 [255 -NH_2, CN] (100), 194 [213 –F] (21) ; Anal. Calcd% for $C_{19}H_{15}N_2OSF$338 (found) C 67.45 (67.41); H4.44 (4.39); N 8.28 (8.26); S 9.47(9.47) F 5.62 (5.60).

2-Amino -4-(5-chloro-2-furyl) -10-fluoro-4,5,6,7 –tetrahydrobenzo[6,7] –cyclohepta[1,2-b]pyran-3-carbonitrile (3_c)

Yield (78%); m.p.120.1-121.4ºC (pet.ether 40-60 ºC); IR (KBr, cm^{-1}) : 3410, 3370 (NH_2) and 2210 (CN) ; ^{1}H NMR ($CDCl_3$) δ : 7.3-7 (m, 3H, Ar –H), 6.28-6.27 (d, 1H, of furan protons), 6.13-6.12(d, 1H, of furan protons), 4.62 (s, 2H, NH_2), 4.21 (s, 1H, pyrane proton), and 2.9- 1.7 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%) : 357.5 [M^+] (100), 255 [M^+ -C_4H_2OCl] (35), 213 [255 -NH_2, CN] (66), 194[213 –F] (14); Anal. Calcd% for $C_{19}H_{15}N_2O_2$ F Cl 357.5 (found) C 63.78 (63.76); H4.19 (4.15); N 7.83 (7.79) F 5.31 (5.30),Cl 9.93(9.91).

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

To a mixture of compounds **(2_{a-c})** (5mmol) and phenyl hydrazine (0.54g, 5 mmol) in absolute ethanol (50ml, few drops of triethylamine (TEA) are added as a catalyst. The reaction mixture is refluxed for 8h, after cooling, the formed solid is collected by filtration, dried and crystallized from the suitable solvent to give the corresponding pyrazole derivatives **(4_{a-c})**.

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

Yield (91%); m.p. 204.1 – 205.7º C (ethanol); IR (KBr, cm^{-1}) : 1598 (C=N) ;^{1}H NMR (C DCl_3) δ : 8.65-8.63(d, 2H, of pyridine -H),8.62-8.61 (d, 2H, of pyridine -H),7.67-6.84 (m, 8H, Ar –H) 4.75-4.73(d, $1H_a$,pyrazole H), 4,71- 3.25 (m,3H, H_b + CH_2, cycloheptene ring), and 3.20-1.80 (m, 4H,CH_2, cycloheptene ring); MS, m/z (%) : 357 [M^+] (89), 279 [M^+ -C_5H_4N] (100), 202 [279-C_6H_5] (36) and 183 [202 –F] (22); Anal. Calcd% for $C_{23}H_{20}N_3$ F357 (found) C 77.31 (77.29) ;H5.60 (5.59); N 11.76 (7.70) F 5.32 (5.31).

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

Yield (90%); m.p. 162.8-163.6 Cº(n-hexane); IR

(KBr, cm^{-1}) : 1598 (C=N) ; ^{1}H NMR (C DCl_3) δ : 7.7(s, 1H, of thiophene-H),7.7-7.69 (d, 1H, of thiophene-H), 7.4-7.35 (d, 1H, of thiophene-H), 7.23-6.82 (m, 8H, Ar –H), 7.6-7 (m, 3H, of thiophene-H) 4.34-4.31 (d, $1H_a$, pyrazole- H), 3.30-2.56(m,3H, H_b +CH_2,cycloheptene ring), and 2. 29- 1.80 (m, 4H, $2CH_2$ of cycloheptene ring);MS, m/z (%) : 362[M^+] (93), 279 [M^+ -C_4H_3S] (88), 202 [279- C_6H_5] (100) and 183 [202 –F] (28); Anal. Calcd% for $C_{22}H_{19}N_2$ S F 362(found) C 72.93 (72.90) ; H 5.25 (5.21) ; N 7.73 (7.69) S 8.83 (8.78); F5.25 (5.21).

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

Yield (85%); m.p. 129.8-130.5 ºC (n-hexane) ;IR (KBr, cm^{-1}) : 1598 (C=N); ^{1}H NMR (C DCl_3) δ :7.6-6.6(m, 8H, Ar –H), 6.5 (d, 1H, of furan-H), 6.3(d, 1H, of furan-H), 5.42 (d,$1H_a$,pyrazole- H), 3.3-2.6 (m,3H, H_b + CH_2, cycloheptene ring), and 2.2- 1.9 (m, 4H, $2CH_2$ of cycloheptene ring); MS, m/z (%) : 380.5 [M^+] (57), 279 [M^+ -C_4H_2OCl] (100), 202 [279 –C_6H_5] (49), 183[202 –F] (26); Anal. Calcd% for $C_{22}H_{18}N_2OFCl$ 380.5(found) C 85.57 (85.49) ;H 4.73 (4.69) ; N 7.37 (7.30) F 4.99 (4.96),Cl 9.33(9.31).

Synthesis of 10- fluoro-4-aryl- 1,3,4,5,6,7-hexahydrobenzo-[6,7]cyclohepta[1,2-d] pyrimidine-2-thione derivatives (5_{a-c})

A mixture of **(2_{a-c})** (10 mml) and thiourea (0.76g, 10 mmol) in ethanolic potassium hydroxide (2g KOH in 100ml ethanol) is refluxed for 9 h. The formed precipitate is filtered off, washed with water, dried and crystallized from the proper solvent to give **(5_{a-c})**, respectively.

10- Fluoro-4-(4-pyridinyl)- 1,3,4,5,6,7-hexahydrobenzo-[6,7]cyclohepta[1,2-d] pyrimidine-2-thione (5_a)

Yield (88%); m.p.2.3-113.8 ºC (ethanol) ; IR (KBr, cm^{-1}) : 3434,3259 (2NH); ^{1}H NMR ($CDCl_3$) δ; 9.6, 8 (2s, 2 H, 2NH,D_2O exchangeable), 8.62 (d, 2H, of pyridine protons), 7.38(d, 2H, of pyridine protons), 7.3-7.1 (m, 3H, Ar –H), 4.40 (s,1H, pyrimidine–H)and 2.9-2 (m,6H,$3CH_2$of cycloheptene ring) ;MS, m/z (%) : 325 [M^+] (39), 247 [M^+ -C_5H_4N] (100), and 228[247 –F] (41); Anal. Calcd%for $C_{18}H_{16}N_3$ S F 325(found) C 66.46 (66.42); H 4.92 (4.88) ; N 12.92 (12.89); S 9.85 (9.83);F 5.85 (5.80).

10- Fluoro-4-(3-thienyl)- 1,3,4,5,6,7-hexahydrobenzo-[6,7]cyclohepta[1,2-d] pyrimidine-2-thione (5_b)

Yield (89%); m.p 146.1-147.7 ºC (pet.ether80-100ºC); IR (KBr, cm^{-1}) : 3434,3259 (2NH); ^{1}H NMR ($CDCl_3$) δ : 10.3,9.8(2s, 2H, 2NH, D_2O exchangeable), 7.98 (s, 1H, ofthiophene),7.6-7.5(d, 1H, ofthiophene), 7.2-6.9 (d, 1H, ofthiophene) 7.6-7.1 (m, 3H, Ar –H), 5.40 (s, 1H, pyrimidine –H) and 2.8 - 1.5 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%) : 330 [M^+] (100), 247 [M^+ -C_4H_3S] (72) and 228[247 –F] (65); Anal. Calcd% for $C_{17}H_{15}N_2S_2$ F 330 (found) C 61.82 (61.79); H 4.55 (4.51); N 8.48 (8.44); S 19.39 (19.34); F 5.76 (5.75).

10-Fluoro-4-(5-chloro-2-furyl)- 1,3,4,5,6,7 –hexahydrobenzo-[6,7]cyclohepta[1,2-d] pyrimidine-2-thione (5_c)

Yield (83%); m.p127.6- 128.2 ºC (n-hexane) ; IR (KBr, cm^{-1}) : 3434,3259 (2NH); ^{1}H NMR ($CDCl_3$) δ : 10.5, 9.1 (2s, 2 H, 2NH, D_2O exchangeable), 7.4-7.1 (m, 3H, Ar –H), 6.8-6.6 (d, 1H, of furan - H),6.4-6.26 (d, 1H, of furan - H), 5.40 (s, 1H, pyrimidine –H) and 2.8 - 1.5 (m, 6H, $3CH_2$ of cycloheptene ring) ; MS, m/z (%) : 348.5[M^+] (67), 247 [M^+ -C_4H_2OCl] (100) and 228[247 -F] (70); Anal. Calcd% for $C_{17}H_{14}N_2OS$ FCl 348.5 (found) C 58.54 (58.48); H 4.02 (4.02); N 8.03 (8); S 9.18 (9.15); F 5.45 (5.42); Cl10.19(10.18).

Synthesis of 10- fluoro-4-aryl- 1,3,4,5,6,7-hexahydrobenzo-[6,7]cyclohepta[1,2-d] pyrimidine-2-one derivatives (6_{a-c})

A mixture of **(2_{a-c})**(10 mml) and urea (0.60g, 10 mmol) in ethanolic potassium hydroxide (2g KOH in 100ml ethanol) is refluxed for 8 h. The reaction mixture is poured onto water and the obtained precipitate is filtered off, washed with water, dried and crystallized from the proper solvent to give **(6_{a-c})**, respectively.

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

Yield (65%); m.p. 215.5-216.2 ºC(benzene); IR

(KBr, cm^{-1}) : 1720 (C=O) and 3434,3259 (2NH); ^1H NMR (C DCl_3) δ : 10,9.2(2s, 2 H,2NH, D_2O exchangeable) 8.8-8.6 (d, 2H, of pyridine - H),7.6-7.4(d, 2H, of pyridine - H), 7.3-7.1(m, 3H, Ar –H), 5.40 (s, 1H, pyrimidine –H), and 2.8 - 1.3 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%) : 309 [M^+] (80), 231 [M^+ -C_5H_4N] (100) and212 [231 –F] (38%). Anal.Calcd% for $C_{18}H_{16}N_3OF$309 (found) C 69.90 (69.30) ;H 5.18 (5.15); N 13.59 (13.51); F 6.15 (6.12).

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

Yield (69%); m.p236.5-237.7 Cº (pet.ether 80-100 ºC); IR (KBr, cm^{-1}) : 1725(C=O) and 3434,3259 (2NH); ^1H NMR (C DCl_3) δ : 9.9,8.1 (2s, 2 H, 2NH, D_2O exchangeable), 7.9(s, 1H, of thiophene - H),7.6(d, 1H, of thiophene - H), 7.4(d, 1H, of thiophene - H),7.6-7.1 (m, 3H, Ar –H), 5.2 (s, 1H, pyrimidine –H) and 2.7 - 1.8 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%) : 314 [M^+] (59), 231 [M^+ -C_4H_3S] (100) and 212[230 –F] (57). Anal.Calcd% for $C_{17}H_{15}N_2OSF$ 314 (found) C 64.97 (64.93) ;H 4.78 (4.71); N 8.17 (8.12); S 10.19 (10.14); F 6.05 (6.01).

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

Yield (70%); m.p. 129.7-130.9º C (n-hexane);IR (KBr, cm^{-1}) : 1720 (C=O) and 3434,3259 (2NH);^1H NMR (C DCl_3) δ : 10.1,9.8(2s, 2 H,2NH, D_2O exchangeable), 6.8-6.6(d, 1H, of furan - H), 6.4-6.2(d, 1H, of furan - H) 7.3-7.1(m 3H, Ar –H), 5.40 (s, 1H, pyrimidine –H) and 2.8 - 1.3 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%) : 332.5[M^+] (98), 231 [M^+ -C_4H_2OCl] (100) and 212[231 - F] (60); Anal. Calcd%for $C_{17}H_{14}N_2O_2FCl$332.5 (found) C 61.35 (61.30) ;H 4.21 (4.20) ; N 8.21 (8.18); F 5.71 (5.70); Cl10.67(10.62).

Synthesis 2-amino-4- aryl-10- fluoro- 1,3,4,5,6,7-hexahydrobenzo-[6,7]cyclohepta[1,2-d] pyrimidine derivatives (7_{a-c})

A mixture of **(2_{a-c})** (10 mml) and guanidine hydrochloride (0.96g, 10 mmol) in ethanolic potassium hydroxide (2g KOH in 100ml ethanol) is refluxed for 11 h. The reaction mixture is poured onto water and the obtained precipitate is filtered off, washed with water, dried and crystallized from the proper solvent to give **(7_{a-c})**, respectively.

2-Amino-4- (4- pyridinyl)-10- fluoro- 1,3,4,5,6,7-hexahydrobenzo-[6,7]cyclohepta[1,2-d] pyrimidine (7_a)

Yield 2.53g (82%); m.p. 118.5-119.5 ºC (pet.ether 80-100 ºC) ; IR (KBr, cm^{-1}) : 3380 (NH) and 3345 (NH_2) ; ^1H NMR ($CDCl_3$) δ : 10 (s, 1H, NH, exchangeable with D_2O), 8.7-8.6 (d, 2H, of pyridine- H),7.4-7.3(d, 2H, of pyridine- H),7.7-7.1 (m, 3H, Ar –H), 6.80 (s, 2H, NH_2), 4.6 (s, 1H, pyrimidine –H), and 2.9 - 2 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%) : 308[M^+] (100), 230 [M^+ -C_5H_4N] (29) and 211 [230–F] (77); Anal. Calcd% for $C_{18}H_{17}N_4F$308 (found) C 70.13 (70.12) ;H 5.52 (5.51); N 18.19 (18.15); F 6.17 (6.10).

2-Amino-4- (3- thienyl)-10- fluoro- 1,3,4,5,6,7-hexahydrobenzo-[6,7]cyclohepta[1,2-d] pyrimidine (7_b)

Yield (81%); m.p.128.4-129.1 ºC(n-hexane).IR (KBr, cm^{-1}) : 3380 (NH) and 3345 (NH_2). ^1H NMR (C DCl_3) δ : 10.3 (s, 1H, NH, exchangeable with D_2O), 7.5 (s, 1H, of thiophene- H), 7.44-7.40(2d,2H, of thiophene-H)7.15-7.3 (m, 3H, Ar –H), 6.5 (s, 2H, NH_2), 5.40 (s, 1H, pyrimidine –H) and 2.8 - 1.5 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%) : 313 [M^+] (100), 230[M^+ -C_4H_3S] (34), and 211 [230 -F] (58);Anal. Calcd% for $C_{17}H_{16}N_3SF$ 313 (found) C 65.18 (65.14); H 5.11 (5.10); N 13.42 (13.38); S10.22(10.20);F 6.07 (6.02).

2-Amino-4- (5-chloro-2- furyl)-10- fluoro-1,3,4,5,6,7-hexahydrobenzo-[6,7]cyclohepta[1,2-d] pyrimidine (7_c)

Yield (86%); m.p120.7-122.1º C(n-hexane) ;IR (KBr, cm^{-1}) : 3380 (NH) and 3345 (NH_2); ^1H NMR (C DCl_3) δ : 9.8(s, 1H, NH,D_2O exchangeable), 6.28-6.12 (2d, 2H, of furan- H), 7.1-6.9 (m, 3H, Ar –H), 6.80 (s, 2H, NH_2), 5.40 (s, 1H, pyrimidine – H) and 2.9 - 1.5 (m, 6H, $3CH_2$ of cycloheptene ring); MS, m/z (%) : 331.5 [M^+] (55), 230 [M^+ -C_4H_2OCl] (100) and 211 [230 –F] (17). Anal.Calcd% for $C_{17}H_{15}N_3OFCl$331.5 (found) C 61.54 (61.50); H 4.52 (4.49); N 12.67 (12.60); F 5.73 (5.70); Cl 10.71(10.69).

CONCLUSION

Aryl methylene derivatives **(2)** are used as precursor for the synthesis of a variety of heterocyclic ring systems formed upon reaction with malononitrile, phenyl hydrazine, thiourea, urea and guanidine hydrochloride 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.

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REFERENCES

[1] C.B.Begg; Jama, **297**, 953 **(2007)**.
[2] M.S.Abdel Halim, A.A.Nada, W.A.Gad; Monatshefte Fur Chemie, **125**, 14373–1442 **(1994)**.
[3] A.A.Nada, N.R.Mohamed, W.A.Gad, A.W.Erian; Egypt.J.Chem., **43**, 99-105 **(2000)**.
[4] A.G.Hammam, M.Sharaf, N.A.Abdel Hafez; Indian J.Chem., **40B**, 213 **(2001)**.
[5] A.E.Amr, M.M.Abdulla; Indian J.Heteorcycl. Chem, **12**, 129 **(2002)**.
[6] A.G.Hammam, A.F.M.Fahmy, A.E.Amr, A.M.Mohamed; Indian J.Chem., **42B**, 158 **(2003)**.
[7] C.K.Fylaktakidou, J.D.L.Hadjipavlou, E.K.Litinas, N.D.Nicolaides; Curr.Pharm., **10**, 3813 **(2004)**.
[8] J.C.Jung, E.B.Watkins, M.A.Avery; Heterocycles, **65**, 77 **(2005)**.
[9] C.M.Sharaby; Spectrochimica Acta, **66**, 1271-1277 **(2006)**.
[10] A.E.Amr, A.M.Mohamed, S.F.Mohamed, N.A.Abel-Hafez, A.E.F.Hammam; Bioorganic & Medicinal Chem., **14**, 5481-5488 **(2006)**.
[11] N.R.Mohamed, M.M.Abdel Halim, W.A.Gad, F.M.Zaid; Phosphorus, Sulfur, and Silicon, **182**, 551-562 **(2007)**.
[12] M.A.A.Radwan, E.A.Ragab, N.M.Sabry, S.M.El-Shenawy; Bioorganic & Medicinal Chem., **15**, 3832-3841 **(2007)**.
[13] O.O.Fadeyi, S.T.Adamson, E.L.Myles, C.O.Okoro; Bioorganic & Medicinal Chem.Letters, **18**, 4172-4176 **(2008)**.
[14] N.R.T.Gowda, C.V.Kavitha, K.K.Chiruvella, O.Joy, K.S.Rangappa, S.C.Raghavan; Bioorganic & Medicinal Chem.Letters, **19**, 4594-4600 **(2009)**.
[15] K.M.Khan, N.Ambreen, U.R.Mughal, S.Jalil, S.Perveen, M.I.Choudhary; European J.Medicinal Chem., **45**, 4058-4064 **(2010)**.
[16] H.Ren, Sh.Ye, F.Liu, Wuefasternak; J.Tetrahedron, **66**, 8242-8246 **(2010)**.
[17] M.A.M.El-Sharief, Z.Moussa, M.Sh.Ahmed; J.Fluorine Chem., **132**, 596-611 **(2011)**.
[18] P.A.Smith, W.L.Berry; J.Org.Chem., 26,27 **(1961)**.