Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2011, 3(2):48-58
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and Anticancer activity of some novel diphenic acid derivatives

Heba S. A. Elzahabi[1], Mohamed A. Salem[2], Hamdy Kh.Thabet[2]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy (Girls), Al-Azhar University, Nasr City, Cairo, Egypt
[2]Department of Chemistry, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt.

ABSTRACT

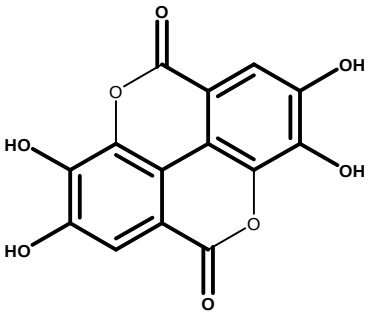
*The reaction of dibenzo[c,e]oxepine-5,7-dione (diphenic anhydride) (**1**) with different aliphatic and aromatic amines **2-4**, **8-10** furnished 2'-[arylcarbamoyl]biphenyl-2-carboxylic acids **5-7, 11, 14** and N2,N2'-diarylbiphenyl-2,2'-dicarboxamide **13.** Condensation reaction of **7** with aromatic aldehydes **15, 16** in ethanol resulted in the formation of Schiff base compounds **17, 18**. Also, reaction of **7** with ethyl/phenylisothiocyanates **19, 20** in dioxane afforded thiourea derivatives **22, 23**. Reaction of **7** with chloroacetylchloride furnished the intermediate chloroacetamide derivative **24** which underwent subsequent cyclization when reacted with malononitrile and potassium thiocynate to afford pyrrole and 4-thiazolidinone compounds **26, 28** respectively. Ten newly synthesized compounds were selected by National Cancer Institute (NCI), USA to be screened for their anticancer activity at a single high dose (10^{-5} M) against a panel of 60 cancer cell line.*

The in-vitro screening revealed mild to moderate anticancer activity against different cell lines.

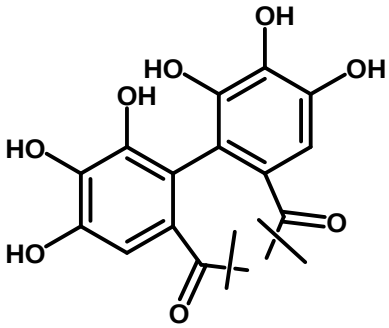
Keywords*:* diphenic acid/ diphenimide/ NCI/ anticancer activity.

INTRODUCTION

Some diphenic acid derivatives that possess useful therapeutic properties have attracted great attention for their widespread in many herbs and components of foods. **Hexahydroxy diphenic acid ester** (polyphenol) and **its ellagic acid** derivative (figure 1) are obtained from dried fruits of **Terminalia bellerica (Bahera)** that are reported to possess analgesic activity [1,2]. Many derivatives of these compounds are also found in blackberries, raspberries and strawberries. The consumption of these fruits is shown to lower the risk of chronic diseases such as cancer, cardiovascular diseases, and other pathologies [3-12].



Ellagic acid (MW302)



HHDP (MW 304)

Figure 1

There is an increasing awareness that health benefits of dietary polyphenols may be due to their role as modulators of cell signaling and gene expression, in addition to their antioxidant activities [13,14]. US Patent provided by Kiely *et al* explored the potential pharmacological role of some novel diphenic acid monoamides. They are reported as leukotriene antagonists, 5-lipoxygenase and mediator release inhibitors providing activity useful for treating asthma, cardiovascular diseases, migraines and immunoinflammatory conditions [15]. Some novel diphenic acid monohydroxamides were equipotent to protypical quinolone, nalidixic acid as DNA Gyrase inhibitors, exhibiting potent antibacterial activity against Escherichia coli. They were preferentialy devoid of the side effects on the central nervous system that has been reported for members of the quinolone series [16]. The biological importance of biaryl diphenic acids extended to their vital role as phospholipase A_2 (PLA_2) inhibitors, owing to their carboxylate groups that linked to a hydrophobic biphenyl system [17]. PLA_2 are known mediators in inflammatory processes and their activity has been linked to many diseases such as asthma, arthritis, psoriasis, pancreatitis. Further, PLA_2 has different physiological functions include their role in cell proliferation and differentiation [18]. The vital biological activity extended to N-(4-methylphenyl)diphenimide as antihyperlipidemic agent. In 1992, this compound successfully lowered serum lipids, very low density lipoprotein (VLDL) and low density lipoprotein (LDL) with elevating high density lipoprotein (HDL) in balanced and hyperlipidemic diet-induced rats [19]. A reliable anticancer activity of some diphenic acid derivatives and diphenimides was reported against several human cancer cell lines e.g. Leukemia, Non-Small Cell Lung Cancer and Breast Cancer [20, 21]. Diphenic acid and its derivatives can not be ignored as interesting moieties for studying the relation between the chemical structure and the physicochemical characters. Conformational analysis of some substituted diphenic acids and diphenimides were investigated. The preferred conformations were chosen by the comparison of experimental and theoretical values of dipole moments [22,23]. Furthermore, some disubstituted diphenic acid esters were used in the preparation of crown ethers. These macromolecules possess ability for complexing certain cation and are useful in phase transfer catalysis [24]. Interestingly, 4,4'-dibromodiphenic acid proved an important role in a number of diverse technologies by using it in the preparation of aromatic, rigid-rod polymers [25]. Motivated by the reported DNA gyrase inhibitory activity, PLA2 inhibitory effect concerning its role in cell proliferation as well as reported anticancer activity of some diphenic acid derivatives [16,20,21], the present study deals with the synthesis of a novel series of diphenic acid monoamides and some diphenimides focusing on their ability to fight cancer. Most of the newly synthesized compounds were selected by National Cancer Institute (NCI) USA to be evaluated for their in-vitro antitumor activity at a single dose assay

(10^{-5} M) on a panel of 60 human cancer cell lines. The novel diphenic acid monoamides carry substituted aryl groups, that vary in the nature and size, covering a large area of electronic, lipophilic and steric environments.

MATERIALS AND METHODS

Chemistry

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (v, cm-^{1}). The ^{1}H NMR spectra were recorded in DMSO-d_6 at 300 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analyses were carried out by the Micro analytical Research Centre, Faculty of Science, Cairo University.

*Reaction of diphenic acid anhydride**1** with aromatic amines (Formation of monoamides **5**, **6**, **7**)*

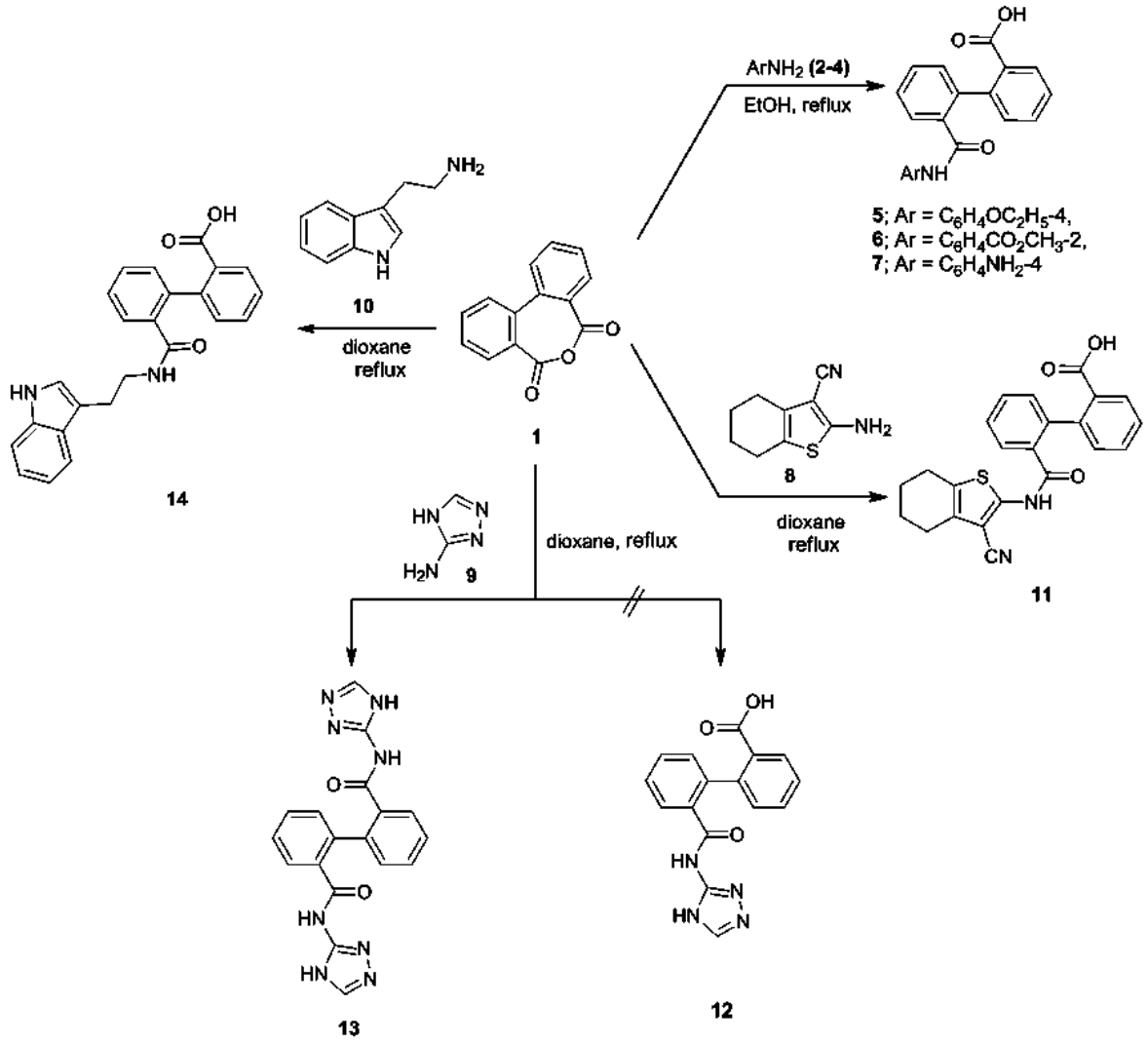
General procedure

A mixture of compound **1** (0.01 mole), appropriate aromatic amines (0.01 mole) in ethanol (30 ml) was refluxed for 3 h. then allowed to cool. The solid product was collected and recrystallized from the proper solvents.

2'-(4-ethoxyphenylcarbamoyl)biphenyl-2-carboxylic acid **5:** Dark brown powder (40%); mp 103-105 °C (EtOH); IR (KBr) cm^{-1} 3559, 3100 (OH, NH), 1715, 1647 (CO); ^{1}H NMR (DMSO-d_6) δ 1.25-1.3 (t, 3H, CH_3), 3.9-3.97 (q, 2H, CH_2) 6.55 (s, D_2O-exchangeable NH), 7.78 (d, *J* = 6 Hz, 2H, Ar*H*), 7.18-7.22 (m, 1H, Ar*H*), 7.27-7.30 (m, 1H, Ar*H*), 7.41-7.50 (m, 6H, 4, 5, 6, 4', 5', 6' biphenyl *H*), 7.60 (d, 1H, 3' biphenyl *H*), 7.80 (d, 1H, *J* = 9 Hz, 3 biphenyl *H*), 9.72 (s, D_2O-exchangeable OH); MS *m/z* (%) 361 (M^+, 84.9), 316 (22.9), 225 (19.25), 108 (100); Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.29; N, 3.88. Found: C, 72.53; H, 5.89; N, 3.32.

2'-(2-(methoxycarbonyl)phenylcarbamoyl)biphenyl-2-carboxylic acid **6:** White powder (36%); mp 110-112 °C (EtOH); IR (KBr) cm^{-1} 3421, 3365 (OH, NH), 1719, 1677 (CO); ^{1}H NMR (DMSO-d_6) δ 3.81 (s, 3H, OCH_3), 7.14-7.26 (m, 5H, 4Ar*H* + D_2O-exchangeable N*H*), 7.42-7.7 (m, 7H, 4, 5, 6, 4', 5', 6' biphenyl *H* + 1H, 3' biphenyl *H*), 7.87 (s, 1H, 3 biphenyl *H*), 12.5 (s, D_2O-exchangeable O*H*); MS *m/z* (%) 375 (M^+, 0.98), 330 (10.30), 298 (44.3), 270 (5.78), 211 (30.63), 151 (100); Anal. Calcd for $C_{22}H_{17}NO_5$: C, 70.39; H, 4.56; N, 3.73. Found: C, 70.11; H, 4.25; N, 3.49.

2'-(4-aminophenylcarbamoyl)biphenyl-2-carboxylic acid **7:** Dark brown powder (42%); mp 208-210°C (EtOH); IR (KBr) cm^{-1} 3431, 3331 (OH, NH, NH_2), 1719, 1685 (CO); ^{1}H NMR (DMSO-d_6) δ 6.40 (d, 2H, *J* = 9 Hz, Ar*H*), 6.97 (d, 2H, *J* = 9 Hz, Ar*H*), 7.12-7.48 (m, 6H, 4, 5, 6, 4', 5', 6' biphenyl *H*), 7.58 (d, 1H, *J* = 6 Hz, 3' biphenyl *H*), 7.76 (d, 1H, *J* = 6 Hz, 3 biphenyl *H*), 9.65 (s, 1 D_2O-exchangeable N*H*), 10.15 (s, 1 D_2O-exchangeable O*H*); MS *m/z* (%) 333 (M^++1, 15.37), 332 (M^+, 61.24), 331 (M^+-1, 0.5), 181 (99), 151 (100). Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.05; H, 4.61; N, 8.28.



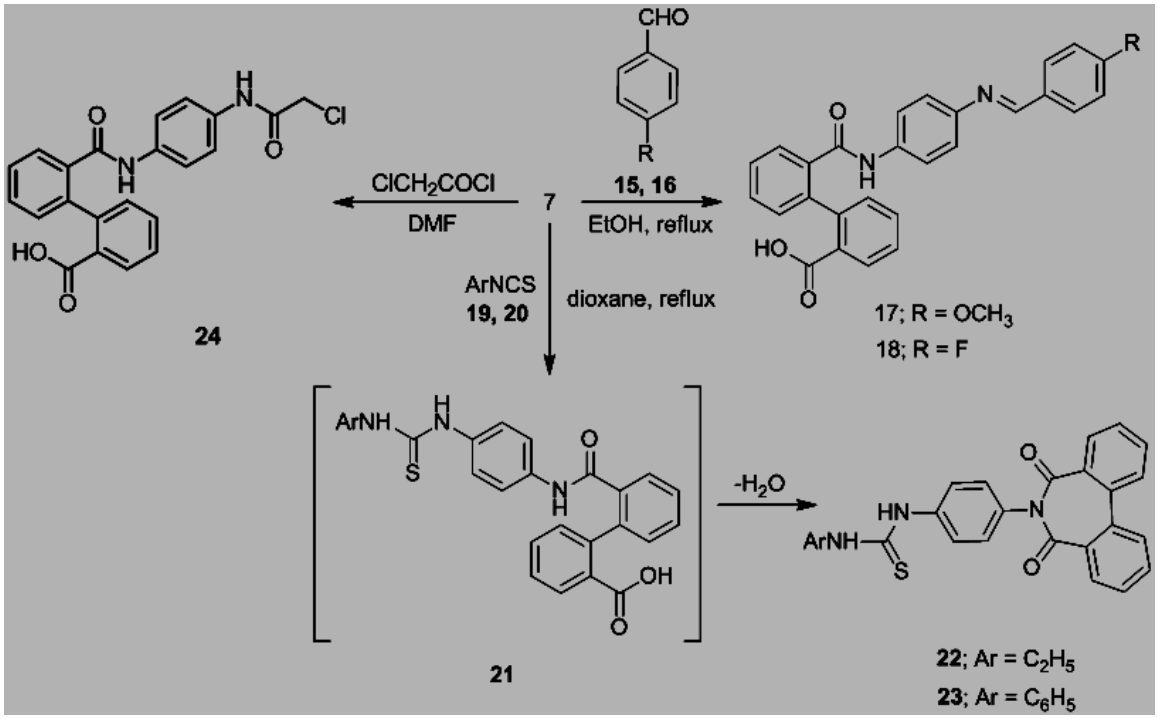
Scheme 1

*Reaction of diphenic acid anhydride **1** with aliphatic or heterocyclic amines (Formation of monoamides **11**, **13**, **14**)*

General procedure

A mixture of compound **1** (0.01 mole), appropriate aliphatic or heterocyclic amines (0.01 mole or 0.02 mole for 2-aminotriazole) in dioxane (30 ml) was refluxed for 3 h. then allowed to cool. The solid product was collected and recrystallized from the proper solvents.

2'-(3-cyano-2,3,4,5,6,7-hexahydrobenzo[b]thiophen-2-yl-carba-moyl)biphenyl-2-carboxylic acid **11:** White fine crystal (60%); mp 129-131 °C (DMF); IR (KBr) cm^{-1} 3446, 3328 (OH, NH), 2197 (CN) 1716, 1682 (CO); ^{1}H NMR (DMSO-d_6) δ 1.67-1.72 (m, 4H, $2CH_2$ beta cyclohexyl *H*), 2.31-2.41(m, 4H, $2CH_2$ alpha cyclohexyl *H*), 3.51 (s, 2H, thiophenyl *H*), 6.91 (s, D_2O-exchangeable N*H*), 7.14-7.22 (m, 2H, 4, 4' biphenyl *H*), 7.44-7.46 (m, 2H, 5,5' biphenyl *H*), 7.55-7.58 (m, 2H, 6,6' biphenyl *H*), 7.85-7.88 (m, 2H, 3, 3' biphenyl *H*), 12.8 (s, D_2O-exchangeable O*H*); MS *m/z* (%) 376 (M^+- CN, 0.48), 313 (1.05), 202 (2.70), 191 (92.05), 149 (100), 135 (95.44); Anal. Calcd for $C_{23}H_{18}N_2O_3S$: C, 68.64; H, 4.5; N, 6.96. Found: C, 68.35; H, 4.29; N, 6.71.



Scheme 2

N2,N2'-di(4H-1,2,4-triazol-3-yl)biphenyl-2,2'-dicarboxamide **13**: White fine crystal (65%); mp 114-116 °C (DMF); IR (KBr) cm^{-1} 3421-3002 (NH), 1697, 1677 (CO); ^{1}H NMR (DMSO-d_6) δ 3.51 (s, 2H, triazolyl *H*), 7.14-7.22 (m, 2H, 4,4' biphenyl *H*), 7.42-7.45 (m, 2H, 5, 5' biphenyl *H*), 7.47-7.58 (m, 4H, 6, 6' biphenyl *H* + D_2O-exchangeable 2N*H*), 7.85-7.89 (m, 2H, 3, 3' biphenyl *H*), 12.4 (brs, D_2O-exchangeable 2N*H*); MS *m/z* (%) 376 (M^++2, 6.3), 212 (14.6), 125 (18.8), 87 (35.4), 50 (100). Anal. Calcd for $C_{18}H_{14}N_8O_2$: C, 57.75; H, 3.77; N, 29.93. Found: C, 57.99; H, 3.59; N, 29.63.

2'-(2-(1H-indol-3-yl)ethyl-carbamoyl)biphenyl-2-carboxylic acid **14:** Light brown powder (50%); mp 122-124 °C (DMF); IR (KBr) cm^{-1} 3397-3250 (OH, NH), 1704, 1602 (CO); ^{1}H NMR (DMSO-d_6) δ 2.49 (t, 2H, C*H*$_2$-CH$_2$-N), 3.24 (t, 2H, CH$_2$-C*H*$_2$-N), 6.93-7.07 (m, 5H, 4 Ar*H* + D_2O-exchangeable indole-N*H*), 7.12 (s, 1H, indole C*H*), 7.30-7.51 (m, 6H, 4, 5, 6, 4', 5', 6' biphenyl *H*), 7.76 (d, 1H, *J* = 9 Hz, 3' biphenyl *H*), 7.86 (s, 1H, 3 biphenyl *H*), 10.73 (s, 1H, D_2O-exchangeable CON*H*), 12.9 (s, 1H, D_2O-exchangeable O*H*); MS *m/z* (%) 384 (M^+, 1.3), 340(16.2), 224 (3.3), 143 (100); Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.69; H, 5.11; N, 7.05.

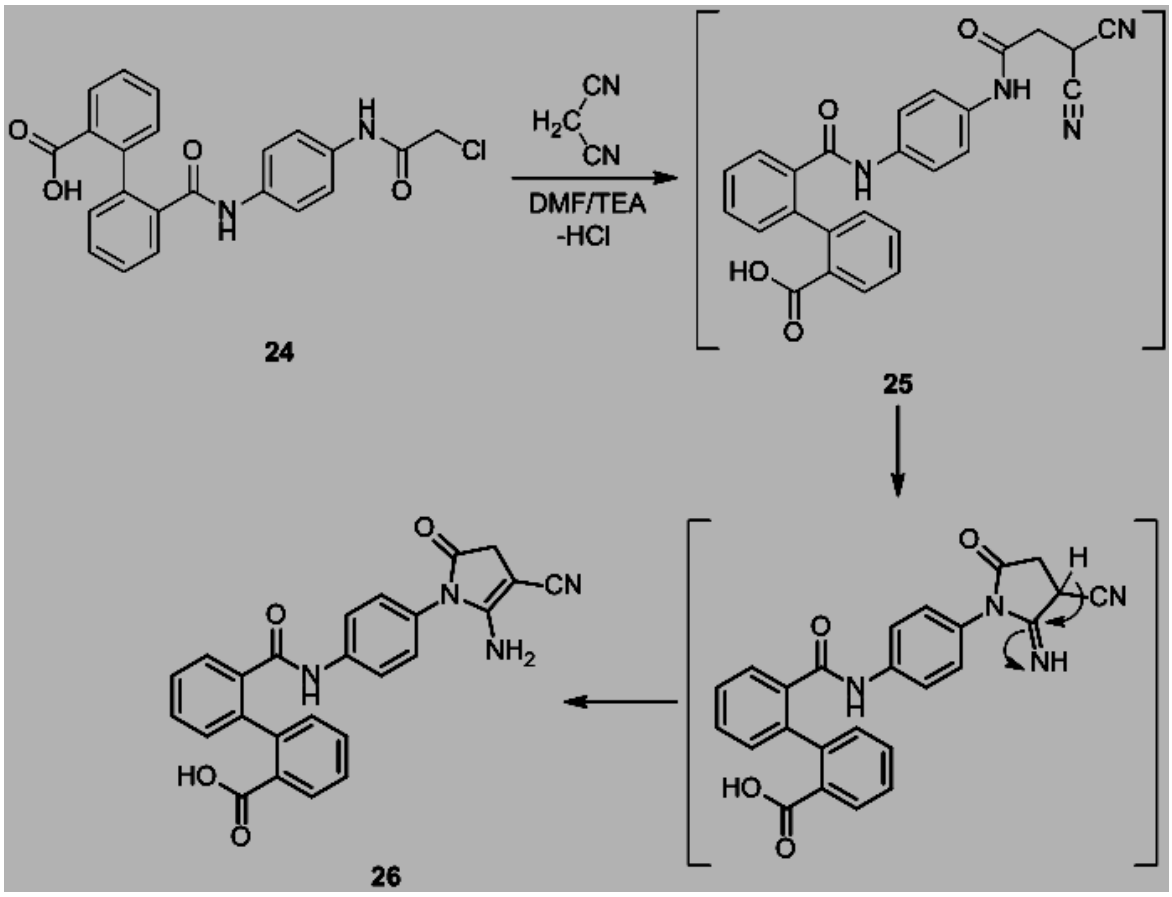
*Reaction of p-aminophenylcarbamoyl compound **7** with aromatic aldehydes **15,16** (Formation of Schiff derivatives **17**, **18**)*

General procedure

A mixture of compound **7** (0.01 mole), appropriate aromatic aldehydes (0.01 mole) in ethanol (30 ml) was refluxed for 3 h. The solid product which separated during reflux, was collected and recrystallized from the proper solvents.

(Z)-2'-(4-(4-methoxybenzylideneamino)phenylcarbamoyl)-biphenyl-2-carboxylic acid **17:** Brown powder (70%); mp 197-199 °C (DMF); IR (KBr) cm^{-1} 3425 (OH, NH), 1606 (CO); ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H, OC*H*$_3$), 6.59 (d, 2H, *J* = 9 Hz, Ar*H*), 6.99-7.11 (m, 10H, 4, 5, 4', 5', biphenyl H + 6 Ar*H* + D_2O-exchangeable N*H*), 7.77-7.86 (m, 4H, 3, 6, 3', 6'

biphenyl *H*), 8.46 (s, 1H, C*H*=N), 9.81 (s, D_2O-exchangeable O*H*); MS *m/z* (%) 452 (M^+ + 2, 1.9), 451 (M^+ + 1, 7), 450 (M^+, 14.2), 344 (100), 226 (23.4), 181 (23.7); Anal. Calcd for $C_{28}H_{22}N_2O_4$: C, 74.66; H, 4.92; N, 6.22. Found: C, 74.41; H, 4.63; N, 5.99.



Scheme 3

(Z)-2'-(4-(4-fluorobenzylideneamino)phenylcarbamoyl)biphenyl-2-carboxylic acid **18:** Buff powder (65%); mp 295-297 °C (DMF); IR (KBr) cm^{-1} 3247, 3060 (OH, NH), 1680, 1598 (CO); ^{1}H NMR (DMSO-d_6) δ 6.47 (d, 2H, *J* = 9 Hz, Ar*H*), 6.94 (d, 2H, *J* = 9 Hz, Ar*H*), 7.14-7.16 (m, 5H, Ar*H* + D_2O-exchangeable N*H*), 7.35-7.57 (m, 6H, 4, 5, 6, 4', 5', 6' biphenyl H), 7.73 (d, 1H, *J* = 9 Hz, 3' biphenyl *H*), 7.94 (d, 1H, *J* = 9 Hz, 3 biphenyl *H*), 9.91 (s, 1H, C*H*=N), 10.01(s, D_2O-exchangeable O*H*); MS *m/z* (%) 439 (M^+ + 1, 10.5), 438 (M^+, 33.5), 420 (2.4), 394 (1.4), 214 (63.2), 181 (100). Anal. Calcd for $C_{27}H_{19}FN_2O_3$: C, 73.96; H, 4.37; N, 6.39. Found: C, 73.73; H, 4.19; N, 6.21.

*Reaction of p-aminophenylcarbamoyl compound **7** with isothiocyanates **19**, **20** (Formation of thiourea derivatives **22**, **23**)*

General procedure

A mixture of compound **7** (0.01 mole), appropriate isothiocyanate (0.01 mole) in dioxane (30 ml) was refluxed for 3 h. Then allowed to cool. The solid product was collected and recrystallized from the proper solvents.

1-(4-(5,7-dioxo-5H-dibenzo[c,e]azepin-6(7H)-yl)phen-yl)-3-ethylthiourea **22:** Grey powder (36%) mp 222-224 °C (EtOH); IR (KBr) cm^{-1} 3261 (NH), 1691 (CO), 1124 (CS); ^{1}H NMR (DMSO-d_6) δ 1.04-1.13 (t, 3H, CH_3), 3.47-3.51 (q, 2H, CH_2), 7.31-7.37 (m, 12H, 4 Ar*H* + 8

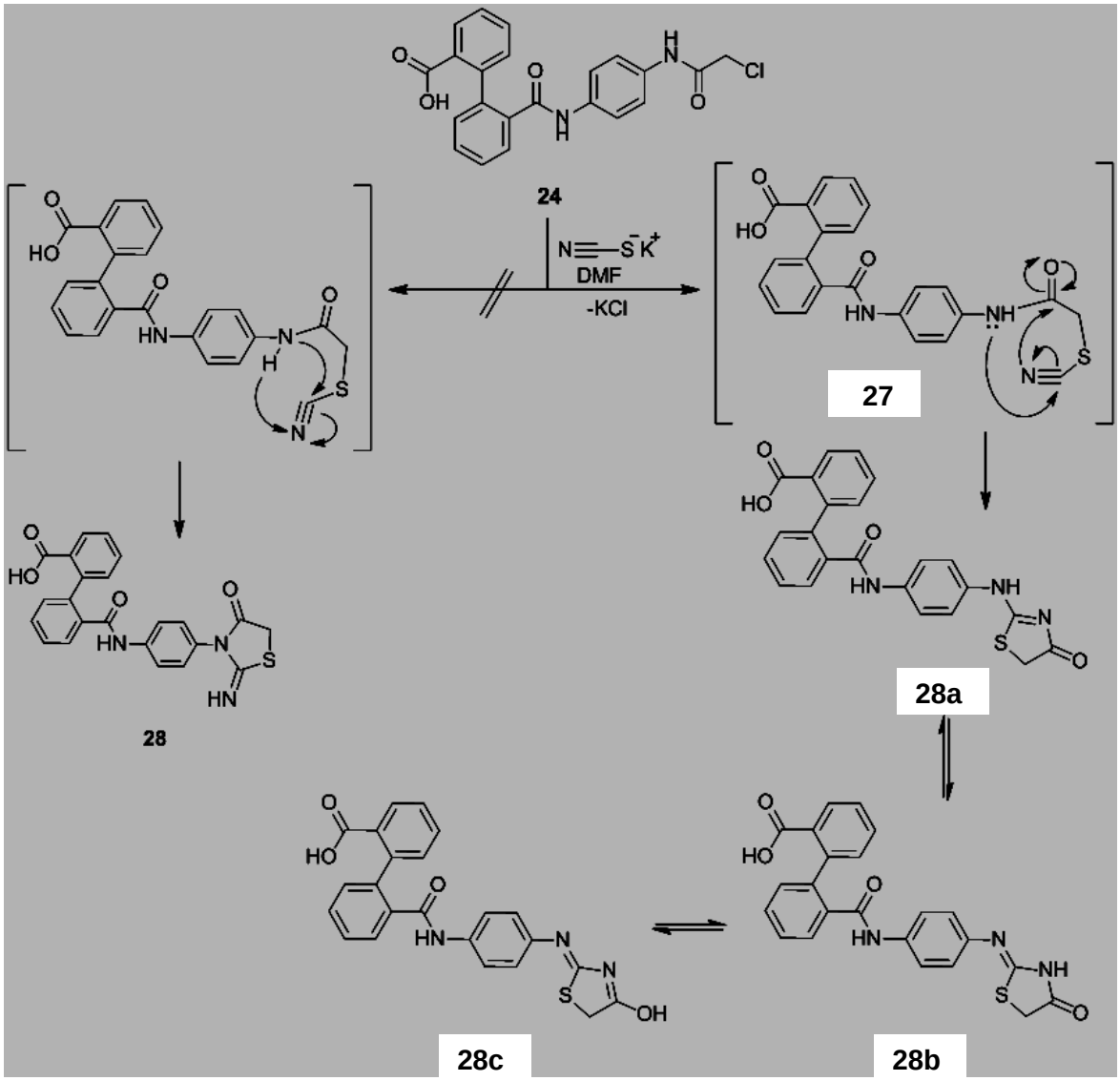
biphenyl *H*), 7.62, 9.35 (2s, 2H, D_2O-exchangeable 2 N*H*); MS *m/z* (%) 401 (M^+, 0.59), 372 (0.61), 357(0.59), 298 (0.82), 214 (20.39), 196 (10.75), 180 (73.19), 56 (100); Anal. Calcd for $C_{23}H_{19}N_3O_2S$: C, 68.82; H, 4.77; N, 10.47. Found: C, 68.42; H, 4.29; N, 10.25.

1-(4-(5,7-dioxo-5H-dibenzo-[c,e]-azepin-6(7H)-yl)phenyl)-3-phenylthiourea **23:** Brown powder (40%); mp 248-250 °C (EtOH); IR (KBr) cm^{-1} 3268 (NH), 1684 (CO), 1115 (CS); ^{1}H NMR (DMSO-d_6) δ 7.09-7.14 (m, 3H, Ar*H*), 7.30-7.35 (m, 4H, Ar*H*), 7.44-7.50 (m, 10H, 2Ar*H* + 8 biphenyl *H*), 9.73 (s, 2H, D_2O-exchangeable 2N*H*); MS *m/z* (%) 451 (M^+ + 2, 1.5), 450 (M^+ + 1, 1.8), 240 (4.4), 180 (8.8), 126 (11), 60 (100). Anal. Calcd for $C_{27}H_{19}N_3O_2S$: C, 72.14; H, 4.26; N, 9.35. Found: C, 71.89; H, 4.09; N, 9.06.

2'-(4-(2-chloroacetamido)phenylcarbamoyl)biphenyl-2-carboxylic acid **24:** To a solution of compound **7** (0.01 mole) in dimethylformamide (30 ml), Chloroacetyl chloride (0.01 mole) was added in dropwise manner with stirring at room temperature for 1 h, then the reaction mixture was poured into ice/water and acidified with 0.1 N HCl at pH 3-4. the resulting precipitate was filtered off, dried and recrystallized from ethanol to yield **24** in dark brown powder (50%); mp >300 °C; IR (KBr) cm^{-1} 3305, 3248 (OH,NH), 1767, 1671 (CO); ^{1}H NMR (DMSO-d_6) δ 4.2 (s, 2H, COCH_2Cl), 7.18-7.22 (m, 6H, 4Ar*H* + D_2O-exchangeable 2N*H*), 7.25-7.52 (m, 6H, 4, 5, 6, 4', 5', 6' biphenyl *H*), 7.60 (d, 1H, *J* = 6 Hz, 3' biphenyl *H*), 7.80 (d, 1H, *J* = 6 Hz, 3 biphenyl *H*), 9.76 (s, D_2O-exchangeable O*H*); MS *m/z* (%) 408 (M^+, 0.21), 364 (2.30), 343 (0.6), 248 (7.43), 224 (35.85), 197 (51.02), 180 (100), 116 (2.75), 114 (6.78); Anal. Calcd for $C_{22}H_{17}ClN_2O_4$: C, 64.63; H, 4.19; N, 6.85. Found: C, 64.42; H, 4.29; N, 6.59.

2'-(4-(4-amino-5-cyano-2-oxo-2,3-dihydro-1H-pyrrol-1-yl) phenylcarbamoyl)biphenyl-2-carboxylic acid **26:** A suspension of compound **24** (0.01 mole), malononitrile (0.01 mole) and triethylamine (0.01 mole) in dimethylformamide (20 ml) was heated under reflux for 6 h, after cooling to room temperature the resulting precipitate was filtered off, dried and recrystallized from dioxane to yield **26** as dark brown powder (40%); mp >300 °C; IR (KBr) cm^{-1} 3433, 3294 (OH, NH, NH_2), 2212 (CN), 1742, 1641 (CO); ^{1}H NMR (DMSO-d_6) δ 2.49 (s, 2H, 2,3-dihydropyrrol CH_2), 7.17-7.19 (m, 2H, 4, 4', biphenyl *H*), 7.24 (s, 1H, D_2O-exchangeable N*H*), 7.27-7.51 (m, 8H, 4 Ar*H* + 5, 6, 5', 6' biphenyl *H*), 7.59 (d, 1H, *J* = 9 Hz, 3' biphenyl *H*), 7.78 (d, 1H, *J* = 9 Hz, 3 biphenyl *H*), 9.82 (s, 2H, D_2O-exchangeable NH_2), 9.89 (s, 1H, D_2O-exchangeable O*H*); MS *m/z* (%) 434 (M^+- 4, 9), 296 (7.5), 225 (23.9), 181 (53.7), 180 (95.5), 152 (100); Anal. Calcd for $C_{25}H_{18}N_4O_4$: C, 68.49; H, 4.14; N, 12.78. Found: C, 68.19; H, 4.29; N, 12.52.

2'-(4-(2-imino-4-oxo-1,3-thiazolidin-3-yl)phenylcarbamo-yl)biphenyl-2-carboxylic acid **28:** A suspension of compound **24** (0.01 mole) and potassium thiocyanate (0.01 mole) in dimethylformamide (20 ml) was heated under reflux for 1 h, after cooling the reaction mixture is poured into water (100 ml), the precipitate is separated by filtration, washed with water and recrystallized from dioxane to give **28** as dark brown powder (41%); mp >300 °C; IR (KBr) cm^{-1} 3407, 3280 (OH, NH), 1714 (CO); ^{1}H NMR (DMSO-d_6) δ 3.78 (s, 2H, 1,3-thiazolidine CH_2), 7.16 (m, 2H, 4,4', biphenyl *H*), 7.24 (s, 1H, D_2O-exchangeable N*H*), 7.36-7.50 (m, 8H, 4Ar*H* + 5, 6, 5', 6' biphenyl *H*), 7.59 (d, 1H, *J* = 9 Hz, 3' biphenyl *H*), 7.79 (d, 1H, *J* = 9 Hz, 3 biphenyl *H*), 9.88 (s, D_2O-exchangeable C=N*H* + O*H*); MS *m/z* (%) 431 (M^+, 0.5), 387 (0.1), 358 (1.1), 332 (30.7), 181 (58.6), 108 (100); Anal. Calcd for $C_{23}H_{17}N_3O_4S$: C, 64.03; H, 3.97; N, 9.74. Found: C, 63.77; H, 4.12; N, 9.47.



Scheme 4

RESULTS AND DISCUSSION

Chemistry

Diphenic anhydride **1** was prepared by cyclodehydration of diphenic acid according to the reported procedures [26]. Respective diphenic acid monoamides **5-7** were prepared by treating ethanolic solution of diphenic anhydride **1** with equimolar amounts of the appropriate aromatic amines **2-4** under reflux condition. Aminolysis of **1** by aliphatic and heterocyclic amines **8, 10** upon changing the ethanol to dioxane under reflux, afforded the final monoamides **11, 14**. Thin layer chromatography (TLC) study of the reaction of diphenic anhydride **1** with 2-aminotriazole **9**, evidenced the presence of spot corresponding to unreacted starting compound **1**, so it was more convenient to start this reaction with two mole equivalents of **9** to get a single spot, that represents the biphenyl dicarboxamide derivative **13**. Spectral and elemental analysis were in agreement with the proposed structures (scheme 1).

4-Aminophenyl carbamoyl derivative **7** was employed as key intermediate for further synthesis of the other target compounds. Thus when compound **7** was condensed with aromatic aldehydes (namely, p-methoxy and p-fluorobenzaldehydes **15, 16**) in ethanol under reflux afforded the corresponding Schiff compounds **17** and **18** respectively. The azepine derivatives **22, 23** were obtained via the reaction of compound **7** with isothiocyanates **19, 20**. The formation of azepine derivatives was assumed to proceed via initial nucleophilic attack of *p*-amino group of compound **7** on the isothiocyanates functional group to afford non-isolable intermediate **21** which underwent cyclodehydration. Also, compound **7** was reacted with chloroacetyl chloride in recently distilled dimethylformamide (DMF) at room temperature to afford chloroacetamide derivative **24** in a good yield (scheme 2).

Chloroacetamide group of compound **24** was used as a key moiety to introduce pyrrole and thiazolidinone rings, linked to the phenylcarbamoyl side chain affording compounds **26** and **28** respectively. So, compound **24** was refluxed with malononitrile in dimethylformamide, in the presence of triethylamine adopting the reported reaction condition [27] to afford the pyrrole derivative **26** (scheme 3). IR spectrum of **26** was characterized by the presence of NH_2, C≡N, and C=O absorption bands. The ^1H NMR spectrum showed a singlet assigned to the CH_2 group of the pyrrole ring.

Synthesis of compound **26** was assumed to proceed via initial alkylation of malononitrile with elimination of one molecule of HCl [28] to afford non-isolable intermediate **25**. Intramolecular cyclization and tuatomerization of **25** afforded the final pyrrole derivative **26**.

Reaction of compound **24** with potassium thiocyanate in refluxing DMF was attempted to form the non-isolable intermediate **27** that was cyclized on the basis of the mechanism suggested by Vicini et al [29], forming the final thiazolidinone compound **28** as outlined in scheme 4. Elemental and spectral analysis were consistent with the proposed structures.

Anticancer activity

Among the newly synthesized analouges, ten compounds **5**, **7**, **13**, **14**, **18**, **22-24**, **26**, **28** (NCS No. **752444-752448**, **752450-752454**) were selected by National Cancer Institute (NCI) in-vitro disease-oriented human cell screening panel assay to be evaluated for their in-vitro antitumor activity. The effective one-dose assay has been added to the NCI in order to increase the compound throughput and reduce data turnaround time to suppliers while maintaining efficient identification of active compounds [30-32]. In this programme, the selected compounds were screened at a single dose assay 10^{-5} M against 60 human cancer cell subpanel that belong to nine cancer types including leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer cell lines. The data are reported as a mean graph of the percent growth of treated cells. Only compounds which satisfy pre-determined threshold inhibition criteria would progress to the five dose screen.

The recorded data revealed that most of the tested cell lines are resistant to the selected compounds, while some of them showed mild to moderate sensitivity against some compounds. Non-small cell lung cancer, NCI-H522 cell line showed mild sensitivity towards compounds **7**, **24**, **26**, **28** (GI 17.27, 30.08, 28.85, 20.87% respectively). Simultaneously, HOP-92 cell line exhibited mild sensitivity against compounds **13** and **28** (GI value 18.35, 17.31% respectively). Except for the previous cell lines the rest of Non-small cell lung cancer subpanel exhibited high resistance against tested compounds. Regarding Leukemia subpanel cell lines, all of them were resistant to tested compounds except for HL-60(TB) subpanel cell line, that was moderately sensitive towards compounds, **7** (GI 35.65%) and **28** (GI 35%) and

mildly sensitive towards the analogue **26** (27.01%). Also, Leukemia SR cell line showed mild sensitivity against compound **24** (GI 18.99%). Among the resistant CNS Cancer subpanel cell line, SNB-75 was the only cell line that showed mild sensitivity against compounds **7**, **14**, **23, 24**, **28** (GI 17.34, 17.29, 14.40, 17.05, 19.27 respectively). Renal Cancer cell lines, A498 showed mild sensitivity against tested compound **14** (GI 24.69%) and UO-31 was mildly sensitive towards compounds **24** and **28** (GI 21.92, 19.27% respectively). The rest of cancer subpanel cell lines that include Colon, Melanoma, Ovarian, Renal, Prostate and Breast cancer exhibited high resistance against selected compounds.

CONCLUSION

The article described a simple nucleophilic reactions of different amines with diphenic acid anhydride **1**, affording novel monoamides **5-7**, **11**, **13**, **14**. *p*-Aminophenylcarbamoyl derivative **7** was a pivotal intermediate for preparation of other novel compounds e.g. **17**, **18**, **22-24**. The second intermediate was chloroacetamide derivative **24** which underwent nucleophilic attack from malononitrile or potassium thiocyanate with subsequent intramolecular cyclization to produce heterocyclic derivatives **26**, **28**.

The selected compounds **5**, **7**, **13**, **14**, **18**, **22-24**, **26**, **28** did not show potent anticancer activity against the tested cell lines. Among them, the most effective compounds are monoamides **7**, **24** and **28** against Leukemia cell line, HL-60(TB) for compounds **7**, **28** and Non-small cell lung cancer, NCI-H522 for compound **24.**

Acknowledgements
Author thank the members of Drug Research and Development, Division of Cancer Research, National Cancer Institute, Bethesda, for the in-vitro anticancer screening.

REFERENCES

[1] S. Kaur, R. K. Jaggi, *Indian Journal of Experimental Biology* **2010**, 48, 925-930.
[2] M. Ali, K. K. Bhutani, *Indian J. Nat. Prod*. **1991**, 7, 16.
[3] K. Aaby, D. Ekeberg, G. Skrede, *J. Agric. Food Chem*. **2007**, 55, 4395-4406.
[4] E. Riboli, T. Norat, *Am. J. Clin. Nutr*. **2003**, 78, 559S-569S.
[5] J. K. Joshipura, B. E. Hu, E. J. Manson, J. M. Stampfer, B. E. Rimm, E. P. Speizer, G. Colditz, A. Ascherio, B. Rosner, D. Spiegelman, C. W. Willett, *Ann. Intern. Med*. **2001**, 134, 1106-1114.
[6] A. L. Bazzano, J. He, G. L. Ogden, M. C. Loria, S. Vupputuri, L. Myers, K. P. Whelton, *Am. J. Clin. Nutr*. **2002**, 76, 93-99.
[7] Ch. Mertz, V. Cheynier, Z. Gunata, P. Brat, *J. Agric. Food Chem.* **2007**, 55, 8616-8624.
[8] H. C. P. Hollman, L. G. M. Heltog, B. M. Katan, *Food Chem*. **1996**, 57, 43-46.
[9] L. Bravo, *Nutr. Rew*. **1998**, 56, 317-333.
[10] S. Sellappan, C. C. Akoh, G. Krewer, *J. Agric. Food Chem*. **2002**, 50, 2432-2438.
[11] Y.S. Wang, S. H. Lin, *J. Agric. Food Chem*. **2000**, 48, 140-146.
[12] L. Wada, B. Ou, *J. Agric. Food Chem*. **2002**, 50, 3495-3500.
[13] G. Williamson, C. Manach, *Am. J. Clin. Nutr*. **2005**, 81, 243S-255S.
[14] L. R. Williams, E. P. J. Spencer, C. Rice-Evans, *Free Radical Biol. Med.* **2004**, 36, 838-849.
[15] Kiely, S. John, Huang, Suchin, *US Patent* **1986**, No. 06/845704.
[16] K. A. Ohemeng, B. L. Podlogar, V. N. Nguyen, J. I. Bernstein, H. M. Krause, J. J. Hilliard, J. F. Barrett. *J. Med. Chem*. **1997**, 40, 3292-3296.

[17] D. M. Springer, J. J. Bronson, M. M. Mansuri, D. O. Nettleton, K. M. Tramposch, *Bioorganic and Medicinal Chemistry Letters* **1996**, 6, 2669-2672.
[18] D. M. Springer, B. Y. Luh, J. J. Bronson, K. E. McElhone, M. M. Mansuri, K. R. Gregor, D. O. Nettleton, P. L. Stanley, K. M. Tramposch, *Bioorganic & Medicinal Chemistry* **2000**, 8, 1087-1109.
[19] I. H. Hall, O. T. Wong, R. Simlot, D. J. Reynolds, *Pharmaceutical Research* **1992**, 9, 1324-1329.
[20] XW. Kong, YH. Zhang, T. Wang, YS. Lai, SX. Peng, *Chem. Biodivers.* **2008**, 5, 1743-1752.
[21] I. Ganjian, M. Khorshidi, I. Lalezari, *J. of Heterocyclic Chem.* **1991**, 28, 1173-1175.
[22] P. A. Botrel, C. R. Guerillot, *Journal De Chimie Physique* **1974**, 71, 1240-1246.
[23] P. A. Botrel, C. R. Guerillot, *Journal De Chimie Physique* **1974**, 71, 1293-1298.
[24] A. M. Costero, C. Andreu, M. Pitarch, R. Andreu, *Tetrahedron* **1996**, 52, 3683-3692.
[25] T. I. Wallow, B. M. Novak, *J. Am. Chem. Soc*. **1991**, 113, 7411-7412.
[26] H. W. Underwood, E. L. Kochmann, *J. Am. Chem. Soc.* **1923**, 45, 3071-3077.
[27] H. Schäfer, K. Gewald, *Monatsh. Chem.* **1989,** 120, 315-322.
[28] U.P. Basu, J. Sikdar, *J. Ind. Chem. Soc.* **1947,** 19, 466-468.
[29] P. Vicini, A. Geronikaki, K. Anastasia, M. Incerti, F. Zani, *Bioorg. Med. Chem*. **2006**, 14, 3859-3864.
[30] M. C. Alley, D. A. Scudiero, P. A. Monks, M. L. Hursey, M. J. Czerwinski, D. L. Fine, B. J. Abbott, J. G. Mayo, R. H. Shoemaker, M. R. Boyd, *Cancer Research* **1988**, 48, 589-601.
[31] M. R. Grever, S. A. Schepartz, B. A. Chabner, *Semin. Oncol*, **1992**, 19, 622-638.
[32] M. R. Boyd, K.D. Paull, *Drug Development Research* **1995**, 34, 91-109.